

# Guide to transitioning from the aPTT to anti-Xa assay to manage heparin infusions; from The Anticoagulation Forum

## Purpose

This document is intended to describe rationale, benefits and challenges associated with using the anti-Xa assay, as well as describe key considerations for switching from aPTT-based heparin management to an anti-Xa-based approach.

While transition to anti-Xa-based heparin management is, in general, a reasonable change in practice for a variety of reasons (which are detailed below), this information may be particularly relevant during the situations where the use of the aPTT may be challenging such as reagents yielding limited target ranges or the COVID-19 pandemic, as it has been shown that the virus itself impacts the aPTT at baseline in some COVID-19 patients, creating challenges in measuring and monitoring unfractionated heparin (UFH).

## General Information

The anti-Xa Assay is a chromogenic assay that measures/detects medications that inhibit activated factor X (Xa). **The anti-Xa Heparin Assay** is commonly used to measure the anticoagulant effect of unfractionated heparin (UFH) using specific calibrators for heparin. The other most commonly used assay to manage heparin infusions is the activated partial thromboplastin time (aPTT). There is often discordance between aPTT and anti-Xa results from the same blood sample which yields differences in protocol-driven heparin infusion adjustments. However, differences in hard clinical outcomes such as bleeding or recurrent thrombosis have not been observed between anti-Xa and aPTT-based UFH management approaches. Several assessments have found that use of anti-Xa-based management results in more rapid attainment of target values with fewer rate adjustments as compared to the aPTT. Currently, the FDA has approved calibrators for anti-Xa heparin and anti-Xa LMWH assays. Calibrators for anti-Xa direct acting oral anticoagulants are in development, but not currently FDA approved.

In recent years, several hospitals have transitioned from aPTT-based heparin management to anti-Xa-based protocols, as the anti-Xa has now become more cost equivocal, is now more readily available, and because of more rapid attainment of target values with fewer adjustments. Additionally, the anti-Xa assay is less vulnerable to underlying non-anticoagulation-related variables. For example, unlike the aPTT, excess acute phase reactants (fibrinogen and factor VIII) should not affect anti-Xa assay results. Similarly, while the aPTT can reflect physiologically unimportant prolongation in the presence of a “lupus inhibitor”, the presence of antiphospholipid antibodies will not affect the anti-Xa result. Occasionally situations exist in which the aXa activity will not accurately reflect the amount of UFH effect present (See table 1).

When using the anti-Xa assay to measure UFH effect, one potential challenge may be the recent use of other anticoagulants. Anticoagulants that inhibit factor Xa activity such as LMWH (enoxaparin, dalteparin) fondaparinux, anti-Xa direct acting oral anticoagulants (DOACs such as apixaban, rivaroxaban, edoxaban, betrixaban) will affect the anti-Xa assay that is used to measure UFH effect. If the UFH-calibrated anti-Xa assay is used to measure the degree of unfractionated heparin activity in the plasma, presence of any other recently ingested FXa inhibitors will contribute to elevations in the anti-Xa assay result and make it difficult or impossible to interpret the results and reliably use them to guide therapy. The anti-Xa elevation caused by these other agents may persist for up to 3 days and may lead to potentially undesirable reductions in heparin infusion rates. The optimal approach to treating or preventing thrombosis in patients recently administered other direct (DOACs) or indirect (LMWH, fondaparinux) anti-Xa agents who require a switch to intravenous heparin has not been established. Reasonable approaches include:

- Adding a baseline UFH-calibrated anti-Xa level (in addition to a baseline aPTT) prior to initiating a heparin infusion to aid in qualitatively identifying presence of any other anti-Xa inhibiting agent
- If the baseline UFH-calibrated anti-Xa result is high enough (e.g. > 0.7 units/ml or qualitatively detectable using the UFH-calibrated anti-Xa assay based on individual lab normals), using an aPTT -based protocol for a few days (depending on how high the level is and the patient's ability to eliminate the DOAC) should be considered
- After a few days, if therapeutic anticoagulation is still needed and use of non-monitored anticoagulants (LMWH, fondaparinux, DOAC) is not possible, transition back to an anti-Xa-based protocol should be considered

In addition, substances interfering with the color/clarity of the patient's blood sample (e.g., bilirubin value > 20 mg/dL, severe hypertriglyceridemia) may alter results.

As with the aPTT, bad sampling technique (drawing from heparin-contaminated lines or hemodiluting the sample) can lead to unexpected (spurious) values. Should this be suspected, a repeat draw from a different site is advised.

## Implementation considerations:

### Multidisciplinary buy-in and support

- **Have all invested disciplines involved: Providers (cardiology, hematology, hospital medicine, vascular surgery, CT surgery, trauma surgery, and others), Pathology/Laboratory (Physician and Coagulation laboratory personnel, Pharmacy (Clinical, Medication safety), Informatics/EMR, Nursing, or quality and safety**
- **Communication to impacted health system personnel is critical (See example of FAQ's below)**
- **Update all related policies or educational materials/competencies for correct terminology (i.e., change aPTT to anti-Xa throughout)**

### Quality/safety

- **Consider any relevant Joint Commission standards/safety goals**
- **Develop a gap analysis or MUE plan to assess any potential areas for improvement**
- **Keep any oversight group (e.g. Pharmacy and Therapeutic committee, Medication Safety, etc.) posted**

### Clinical/EHR/informatics

- **Identify and address any unique device issues (e.g., Impella devices, ECMO, CRRT and heparin purge solutions) that utilize heparin as part of the therapy**
- **Update all related protocols for correct terminology (i.e., change aPTT to anti-Xa throughout)**
- **Establish consistency and incorporate any other processes into the order sets:**
  - **Standardize as much as feasible**
  - **Baseline labs (aPTT and anti-Xa)**
  - **Follow up laboratory measured**
  - **Titration scales**
  - **Notification if selected values are seen (low platelets, excessively high anti-Xa values), or lack of response after 2-3 upward titrations**
  - **Consider establishing cap dosing requiring further assessments prior to exceeding that must be specifically ordered. (e.g., 3,000 units/hr or > 30 units/kg) to avoid ordering errors**
- **Consider an optional aPTT order-set in settings where the anti-Xa may not be preferred (presence of DOAC and elevated baseline anti-Xa)**
- **Ensure that clinicians understand that there may be situations where the PTT provides physiologically important information not reflected in the anti-Xa measurement (possibly relevant but not related to heparin dose). In such situations, less intense heparin therapy (i.e. lower target aXa levels) may be a consideration**
  - **disseminated intravascular coagulation or dilutional coagulopathy**
  - **vitamin K deficiency**
  - **warfarin effect**
  - **severe hepatic dysfunction**

### Education

- **Consider a competency educating staff on the change – keep it practical and simple**
- **Include education on pump programming and nursing scanning/documentation to avoid errors and ensure this information is consistent with order sets**

### Operational

- **On the day of transition to the anti-Xa – coordinate an optimal time with your informatics and clinical staff (e.g. Tuesday morning after shift change) to make the switch**
- **Run a list of all patients on heparin infusions and adjust to the anti-Xa, being aware to sustain the current rate**
- **Notify all affected nurses of the changes**

**Table 1: Situations impacting measured anti-Factor Xa or aPTT results**

Influencing Factors		anti-Factor Xa	aPTT
Preanalytic	Diurnal Variation	↕	↕
	High Citrate Conc. in Tube	↔	↑
	Poor Blood Sampling	↑	↑
	Underfilled Tubes	↔	↑
	Prolong time (> 2 hours) to sample analysis	↓	↓
	Inadequate centrifugation (inadequate platelet removal)	↓	↓
	Gross Hemolysis in Sample	↓	↔
Analytic	Reagent Issues	↕	↕
	Coagulometer	↕	↕
Biologic	AT Deficiency	↓*	↓
	Increase acute phase reactants (↑FVIII, ↑Fibrinogen)	↔	↓
	Increased Heparin binding proteins	↓	↓
	Obesity (↑ Vd)	↓	↓
	Impaired Renal Function (↓ Elimination)	↑	↑
	Liver Disease (↓ Clotting Factors)	↔	↑
	Consumptive coagulopathy	↔	↑
	Lupus Anticoagulant	↔	↑
	Decreased in specific clotting factors (Factor IX, XI, XII, prekallikrein)	↔	↑
	Elderly	↔	↑
	Recent use of other anti-Xa agents (LMWH, Fondaparinux, DOAC)	↑	↔
	Triglyceride > 360 mg/dl	↑	↔
	T Bili > 6.6 mg/dl	↓	↔
	COVID-19	↔	↑

Adapted from Vandiver JW, et al. Pharmacotherapy 2012;32:546-58

**\* Several assay processes exist. Result not affected if aXa assay incorporates antithrombin in the process.**

## Clinical FAQs

### **Question 1: What is the maximum therapeutic target for the anti-Xa Heparin Assay?**

The MAXIMUM therapeutic target is 0.7 units/mL. For cases that may need a higher therapeutic target (other than ECLS), additional system review may be considered.

### **Question 2: Why has the anti-Xa Heparin Assay considered to be a better test than aPTT for monitoring heparin infusion?**

The anti-Xa Heparin Assay is less affected by certain interferences that affect the aPTT assay. These interferences can include: factor deficiencies (e.g. caused by liver dysfunction) or Lupus Anticoagulant (aka lupus inhibitor).

### **Question 3: Why are baseline levels for both aPTT AND the anti-Xa Heparin Assay drawn?**

Aberrant baseline levels may indicate recent non-heparin anticoagulant exposure or underlying coagulopathy. It will allow clinicians to choose which assay may be best to initially manage the heparin infusion. This might additionally prompt the clinician to choose less aggressive anticoagulant therapy (e.g. if a baseline coagulopathy such as DIC is identified in a patient at high risk of bleeding).

### **Question 4: Should I wait for the baseline anti-Xa Heparin Assay and baseline aPTT results to start the heparin infusion?**

No, the heparin infusion should be started immediately after drawing the ordered baseline tests as per current protocol. The baseline results can be applied to future measurement decisions and dosing adjustments.

### **Question 5: When should I draw samples for heparin monitoring?**

Refer to the applicable order set (if available in electronic health record). In general, the anti-Xa Heparin level may be measured 4-6 hours after an infusion start or infusion rate change without a bolus. If a bolus of 2500 units or less is given with the infusion, then the draw is typically done at least 6 hours later. If a bolus over 2500 units is given with the infusion, values may be elevated from the bolus at 6 hours.

### **Question 6: The baseline anti-Xa Heparin Assay (prior to the heparin infusion) is elevated. What do I do?**

Review if the patient was receiving an anticoagulant that inhibits factor Xa (LMWH, Fondaparinux, DOAC) or has a baseline coagulopathy (e.g. from liver failure) that would affect the aPTT. If yes, consultation from a coagulation expert can assist in management decisions. Another option is to repeat the value if the heparin infusion has not already started.

### **Question 7: The baseline aPTT (prior to the heparin infusion) is elevated. What do I do?**

Consider this may be artifact ("lupus inhibitor") or the patient may have a baseline coagulopathy (e.g. from liver failure) that would affect the aPTT (and possibly change the risk-benefit calculus for IV heparin use). Consultation from a coagulation expert can assist in management decisions.

### **Question 8: Both baseline laboratory tests are elevated prior to heparin infusion. What do I do?**

Consultation from a coagulation expert can assist in management decisions.

### **Question 9: What if the patient is not responsive to heparin therapy (e.g. therapeutic range is not achieved even after infusion adjustment x2 per the order set nomogram)?**

Consider antithrombin level (AT) or AT ag testing and consult a coagulation expert. Another consideration is to measure the anti-Xa and/or aPTT 15 minutes after a bolus is given to assess if there is a response when heparin levels are expected to be high. Call pharmacy if the heparin bag was prepared in the pharmacy (versus a pre-manufactured heparin bag) for a new bag.

## Pharmacy Related FAQ's

If you have a pharmacist attached to your service, please reach out to them during the day to provide additional insights to managing heparin infusions.

### **Question 1: What is the therapeutic range for unfractionated heparin (UFH) using the anti-Xa Heparin Assay?**

Refer to each order set for the IV heparin infusion titration instructions that reflect the therapeutic range. The optimal therapeutic range may be indication specific. [Note: The approaches listed below are subjective and not validated in the literature outside the target range of 0.3-0.7 Units/ml].

Routine therapeutic range = 0.3 to 0.7 Units/mL

Low intensity therapeutic range = 0.1 to 0.4 Units/mL

In some settings, targets of 0.3 to 0.5 Units/mL have been considered when bleeding risks are a notable clinical concern. If the thrombosis concerns are high and bleeding low, a 0.5-0.7 target can be considered. This has not been validated in the literature.

For notable bleeding concerns (e.g. is patient where the baseline PTT is prolonged due to profound depletion of normal clotting factors) and/or lower thrombosis risks, the upper limit of the range can be lowered to 0.3 Units/mL.

### **Question 2: Can I manually modify the IV heparin infusion order set and therapeutic range? (If your EMR is set up this way)**

Maximum orderable targets may be considered (e.g. 0.7 U/mL). If the order set can be manually modified, it is important to verify titrations and goal therapeutic range do not overlap.

## Laboratory FAQs

### **Question 1: What sample type is required for the anti-Xa Heparin Assay and what is the sample viability?**

Citrate plasma (plasma from a blue top tube) is the only valid sample. The test must be performed within 2 hours of draw.

### **Question 2: What are limitations of the anti-Xa Heparin Assay?**

The anti-Xa Heparin Assay is a chromogenic test (relies on colorimetric detection), so samples from patients with hemolysis, icterus, or lipemia can have erroneous results.

### **Question 3: What is the availability and turnaround time for the anti-Xa Heparin Assay?**

Note times of availability (e.g. 24/7); Resulted within \_\_\_ hours of sample received in the laboratory (Revise accordingly to your laboratory)

### **Question 4: What is the order name for intravenous unfractionated heparin monitoring?**

Label as per your laboratory has titled

### **Question 5: What is the anti-Xa Heparin Assay measuring?**

The anti-Xa Heparin assay measures the effect of the heparin based on inhibition of Factor X. In most cases, a high 'anti-Xa Heparin assay' result indicates high heparin anticoagulant effect; however such a result might be reported in a patient with very little or no UFH effect if they had recently received a different FXa inhibitor (e.g. rivaroxaban, apixaban; see above).

### **Question 6: Is the 'anti-Xa Heparin Assay' the same as the 'Factor X Assay'?**

No. The 'anti-Xa Heparin Assay' detects heparin effect in patient plasma based on inhibition of Factor X in an assay reagent. The 'Factor X assay' measures a patient's endogenous level of functional Factor X.

### **Question 7: Can this test be used to measure anti-Xa DOACs?**

In the presence of a DOAC, the anti-Xa assay will typically be elevated if a clinically relevant amount of DOAC is present in the plasma. For most assays, a result of  $< 0.1$  would indicate that there is neither significant UFH nor significant DOAC effect present. anti-Xa assays calibrated to the specific agent is preferred. DOAC calibrators are in development, pending FDA approval.

### **Question 9: Can this test be used to measure dabigatran (Pradaxa)?**

No, tests for measuring dabigatran include an Ecarin clotting assay, dilute thrombin time, or thrombin time. aPTT and prothrombin times can be elevated by dabigatran.

### **Question 10: Can this test be used to measure low molecular weight heparin (Lovenox)?**

The correct test for measuring this drug is 'anti-Xa LMWH Assay' which has specifically calibrated for the LMWH in question. Consider consulting a coagulation expert prior to utilizing.

### **Question 11: Can this test be used to measure fondaparinux (Arixtra)?**

Fondaparinux will elevate anti-Xa levels, but a calibrator to fondaparinux should be used. An FDA approved calibrator is not currently available. If an anti-Xa level for fondaparinux is requested, consider consultation with a coagulation expert.

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