TITLE

Anticoagulant Monitoring Recommendations for Patients Receiving Warfarin, Unfractionated Heparin, Low Molecular Weight Heparin, Fondaparinux, Direct Oral Anticoagulants (DOAC), and Direct Thrombin Inhibitors

WARFARIN:

1. Usually monitored by PT/INR. Critical Value for INR is 4.0.
2. If patient has a positive Lupus Anticoagulant and a sufficiently abnormal baseline PT, then the Chromogenic Factor X is recommended. If the patient has a positive Lupus Anticoagulant with a normal baseline PT, the PT generally remains an acceptable test for monitoring Warfarin.
3. Although the relationship is not precise between the INR and the Chromogenic factor X level (r-squared=0.422), in 50 patients receiving oral anticoagulant therapy and having a Chromogenic factor X level between 15-35%, all were found to have an INR between 2.0-4.0.

Reference: McGlasson DL et al. *Blood Coagulation and Fibrinolysis.* 2008, 19:513–517

UNFRACTIONATED HEPARIN

Updated 3/2021

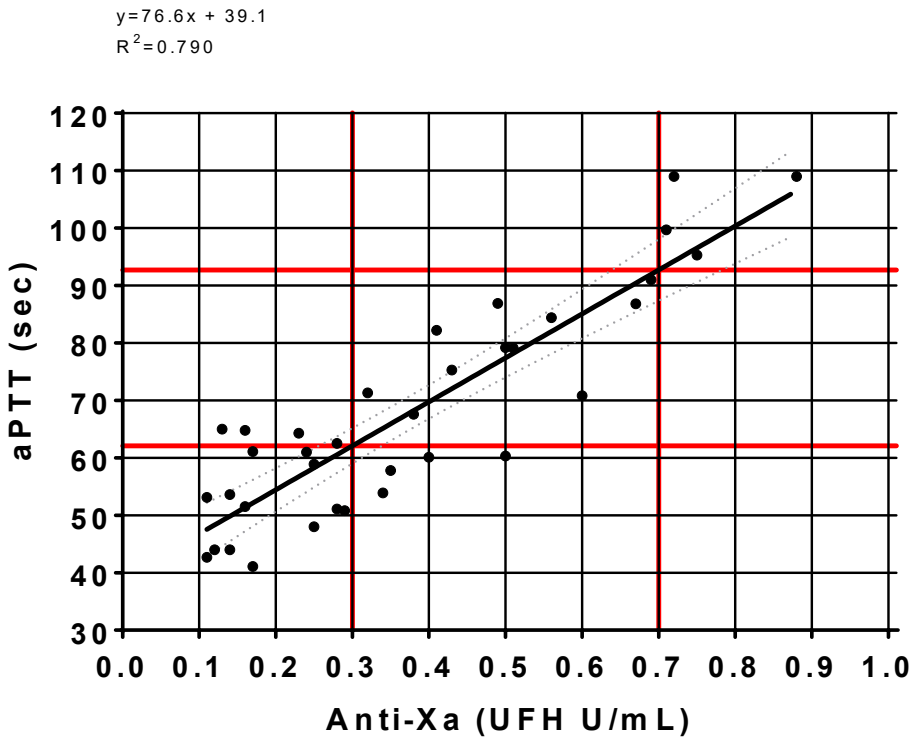
The activated partial thromboplastin time (aPTT) is the test most commonly employed to monitor unfractionated heparin therapy. Some patients, however, have a prolonged baseline aPTT that is not associated with an increased bleeding tendency. For example, this may occur with a lupus anticoagulant or with a deficiency of one of the so-called "contact factors" (factor XII, prekallikrein, or high molecular weight kininogen). In the event that such patients require heparin therapy, an alternative method available to monitor the intensity of their heparin anticoagulation is the anti-Xa heparin assay.

Determination of the intensity of heparin anticoagulation to be employed for an individual patient is a clinical decision that must take into consideration many aspects of that patient's condition. A useful starting point for such determinations can be the general recommendations issued by various medical organizations. Accordingly, for monitoring of heparin therapy with the commonly suggested target range of 0.3-0.7 anti-Xa Units/mL (e.g., for treatment of venous thrombosis), the corresponding aPTT range determined by linear regression analysis of locally obtained population data is currently 62-93 seconds.
Anti-Xa of 0.35 Units/mL corresponds to 66 seconds. For the lower intensity anticoagulation range of aPTT 50-70 seconds (e.g., as in guidelines from the American College of Chest Physicians), the corresponding range is currently 0.14-0.40 anti-Xa Units/mL.

Critical Value for aPTT is > 120 seconds.

Of note, the relationship between aPTT and anti-Xa (see graph below) using the reagent/instrument combination currently in place our laboratory falls well within published norms of such relationships (see, e.g., Cuker A, et al.

2009. Interlaboratory agreement in the monitoring of unfractionated heparin using the anti-factor Xa-correlated activated partial thromboplastin time. J Thromb Haemost. 2009:80-6, PMID: 19017257).



In summary, relationships arising from the current linear regression include the following:

0.3-0.7 anti-Xa units corresponds to 62-93 seconds
0.35 U/mL UFH = 66 sec
50-70 seconds corresponds to 0.14-0.40 anti-Xa units

LOW MOLECULAR WEIGHT HEPARIN

1. Routine monitoring of LMWH is not recommended by the American College of Chest Physicians (Garcia DA et al. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012. 141:e24S).
2. In those instances where LMWH monitoring is undertaken in patients being treated for venous thromboembolism, the ACCP recommends a target range of 0.6-1.0 anti-Xa U/mL.
   From American College of Chest Physicians Guidelines (Chest. 2012 Feb,141(2 Suppl):e24S-e43S. "For treatment of VTE, a conservative peak anti-Xa level with TWICE-DAILY enoxaparin … [measured 4 h after dosing] is 0.6 to 1.0 units/mL. The target range for peak anti-Xa levels (measured 4 h after dosing) with ONCE-DAILY enoxaparin is likely to be above 1.0 units/mL."

FONDAPARINUX:

1. Fondaparinux is monitored using an Anti-Xa assay (sent-out to our reference laboratory).
2. Peak steady-state plasma concentrations are reached approximately 3 hours following injection.
   While there does not appear to be uniform agreement as to ideal therapeutic target intensity, it has been reported that Fondaparinux plasma concentrations obtained in patients treated at prophylactic and therapeutic doses ranged from 0.1-0.5 micrograms/mL. and from 0.6-1.5 micrograms/mL., respectively (J. Thromb. Haemost., 2004, 2:346-379).
   Additionally, in a study reported by the manufacturer of the drug, patients being treated once-daily for DVT had a mean peak steady-state plasma concentrations of approximately 1.2 micrograms/mL. and mean minimum steady-state plasma concentrations of approximately 0.5 micrograms/mL.

RIVAROXABAN:

1. Rivaroxaban is monitored using an anti-Xa assay.
2. Peak steady-state plasma concentrations are typically reached approximately 2 to 3 hours following oral administration.
   Rivaroxaban peak concentrations of 160-360 ng/mL and trough concentrations of 4.3-95.7 ng/mL have been reported in patients taking rivaroxaban 20 mg once daily (Thromb Haemost 2008; 100:453-461); however, actual target goals depend upon intended anticoagulation intensity and dosing schedules for the individual patient.

APIXABAN:

1. Apixaban is monitored using an anti-Xa assay.
2. PT/INR and aPTT are not sensitive to apixaban
3. Peak plasma apixaban concentrations are typically reached approximately 3-4 hours following oral administration. Apixaban half-life is 11-12 hours, assuming normal renal function.
4. Apixaban dosage varies depending on the indication. Therapeutic ranges are not available from the manufacturer. Depending on the dosing regimen, on-treatment Cmax and Cmin levels have been measured/interpolated to be as follows:

2.5 mg, twice daily:
- Cmax geometric mean 62.3 ng/mL (29.7-153.2 ng/mL 5th to 95th percentile)
- Cmin geometric mean 21.0 ng/mL (11.0-89.5 ng/mL 5th to 95th percentile)

5 mg, twice daily:
- Cmax geometric mean 128.5 ng/mL (58.6-302.2 ng/mL 5th to 95th percentile)
- Cmin geometric mean 49.6 ng/mL (21.7-176.5 ng/mL 5th to 95th percentile)

10 mg, twice daily:
- Cmax geometric mean 329.8 ng/mL (111.4-572.4 ng/mL 5th to 95th percentile)
- Cmin geometric mean 103.8 ng/mL (41.1-334.5 ng/mL 5th to 95th percentile)

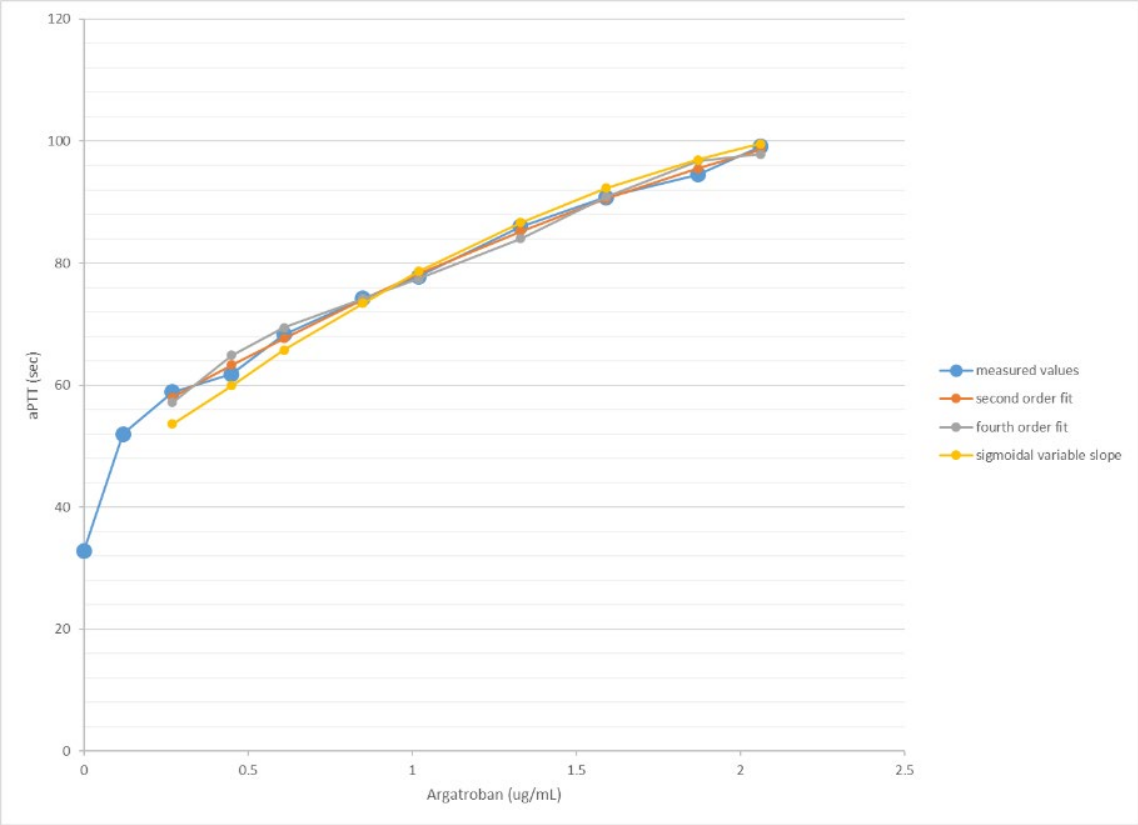
Douxfils J et al. JTH. 2018. 16:209.
Frost et al. Br J Clin Pharmacol. 2013;76:776–86
Byon W et al. CPT Pharmacometrics Syst Pharmacol. 2017. 6:340–349

However, actual target goals depend upon intended anticoagulation intensity and dosing schedules for the individual patient.

ARGATROBAN

1. When baseline aPTT is normal, argatroban can be monitored using the aPTT.
2. Argatroban infusion is typically titrated to achieve an aPTT that is 1.5 – 2.5x the patients's baseline level. Others have advocated 1.5-3x.
3. When baseline aPTT is prolonged (such as in the presence of a lupus anticoagulant or factor deficiency), aPTT can be unreliable in argatroban monitoring.
4. A dilute Thrombin Time-based argatroban measurement should be used whenever the aPTT is unreliable. This test reports a plasma concentration of argatroban in microg/mL, obtained from a standard curve. The reportable range is from 0.2 microg/mL to the highest calibrator level. We no longer provide a derived aPTT value (expected aPTT value for those patients with normal baseline aPTT).

The correlation of aPTT versus argatroban concentration was analyzed by the UCM Coagulation laboratory 1/2020 using a spiking study of normal plasma:



Second order fit best matched the measured values. dTT-based assay does not measure below 0.2 ug/mL argatroban, so those data points were not included in fit.

Argatroban (ug/mL)	Predicted aPTT (sec) by second order curve fit
0.27	58.1
0.45	63.3
0.61	67.7
0.85	74.0
1.02	78.2
1.33	85.2
1.59	90.5
1.87	95.5
2.06	98.6

Argatroban therapeutic target ranges from the literature:

- 0.4-0.8 microg/mL (Colucci G et al. J Transl Sci, 2015. Volume 1(2): 37-42)
  - Based on this single spiking study, would be equivalent to 61.9-72.8 sec
- 0.5-1.5 microg/mL (Seidel H et al. Clinical and Applied Thrombosis/Hemostasis 2018, Vol. 24(2) 287-294)

  - Based on this single spiking study, would be equivalent to 64.7-88.7 sec
- 0.6–1.8 microg/mL (Van Cott EM et al. Semin Thromb Hemost 2017;43:270–276)
  - Based on this single spiking study, would be equivalent to 67.5-94.3 sec
- Approximately 0.5 microg/mL (Warkentin et al. Thromb Haemost. 2005. 94:958)
  - Based on this single spiking study, would be equivalent to 64.7 sec

Current UCM DTI guidance (PGP-36) states "Titrate argatroban infusion to achieve an aPTT that is 1.5 – 2.5 x the baseline level (generally 60-80 seconds), not to exceed 90 seconds."
The equivalent of 60-80 seconds would be 0.34-1.1 ug/mL argatroban.
The equivalent of 90 seconds would be 1.57 ug/mL

It should be kept in mind that the aPTT response to argatroban in an individual patient, particularly one with factor deficiencies or a lupus anticoagulant, could be significantly different than these spiking study results.

5. When switching from a DTI to warfarin, a Chromogenic assay for Factor X can be used to monitor the warfarin effect without interference by the DTI.

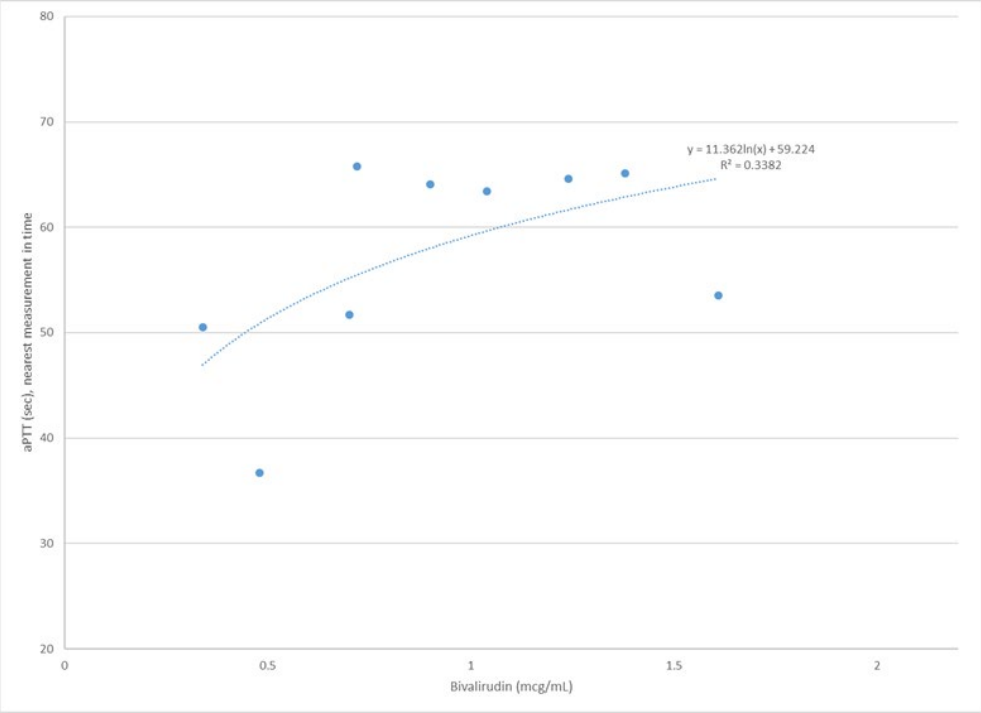
BIVALIRUDIN

Bivalirudin is typically used for short-term anticoagulation (half-life of 25 min) and is not typically monitored. The activated clotting time (ACT) can be used for point-of-care monitoring during procedures.

In situations where longer-term bivalirudin therapy needs to be monitored, the aPTT is not recommended due to poor correlation with drug level (Lind SE et al. Comparison of the aPTT with alternative tests for monitoring direct thrombin inhibitors in patient samples. Am J Clin Pathol. 2014 May;141(5):665-74.)

1. A specific bivalirudin level is available using dilute Thrombin Time-based methodology. This test reports a plasma concentration of bivalirudin in microg/mL, obtained from a standard curve. The reportable range is 0.1 microg/mL to the highest calibrator level.

The response of one patient's aPTT to bivalirudin demonstrates the poor correlation with aPTT with plasma bivalirudin concentration.



Few published bivalirudin therapeutic target ranges are available, and they are somewhat variable:
- Approximately 0.5 microg/mL (Warkentin et al. Thromb Haemost. 2005. 94:958)
- Approximately 1.0 microg/mL (Colucci G et al. J Transl Sci. 2015. 1:37)

2. When switching from a DTI to warfarin, a Chromogenic assay for Factor X can be used to monitor the warfarin effect without interference by the DTI.

ADDITIONALLY:

The Medical Director of the Coagulation Laboratory and their designees are available for consultation in regards to the monitoring of oral anticoagulants, heparin and direct thrombin inhibitors.

The direct oral anticoagulants (DOAC) dabigatran, edoxaban, and betrixaban do not currently have monitoring assays validated for clinical use at UCM.
Contact the Medical Directors of the Coagulation Laboratory or their designee if there is a clinical need to detect presence of these drugs.