TITLE

Patient Care Recommendations for Monitoring Warfarin, Unfractionated Heparin, Low Molecular Weight Heparin, Fondaparinux, Rivaroxaban, Apixaban, and Direct Thrombin Inhibitors

COUMADIN (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 remains an acceptable test for monitoring Coumadin/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.

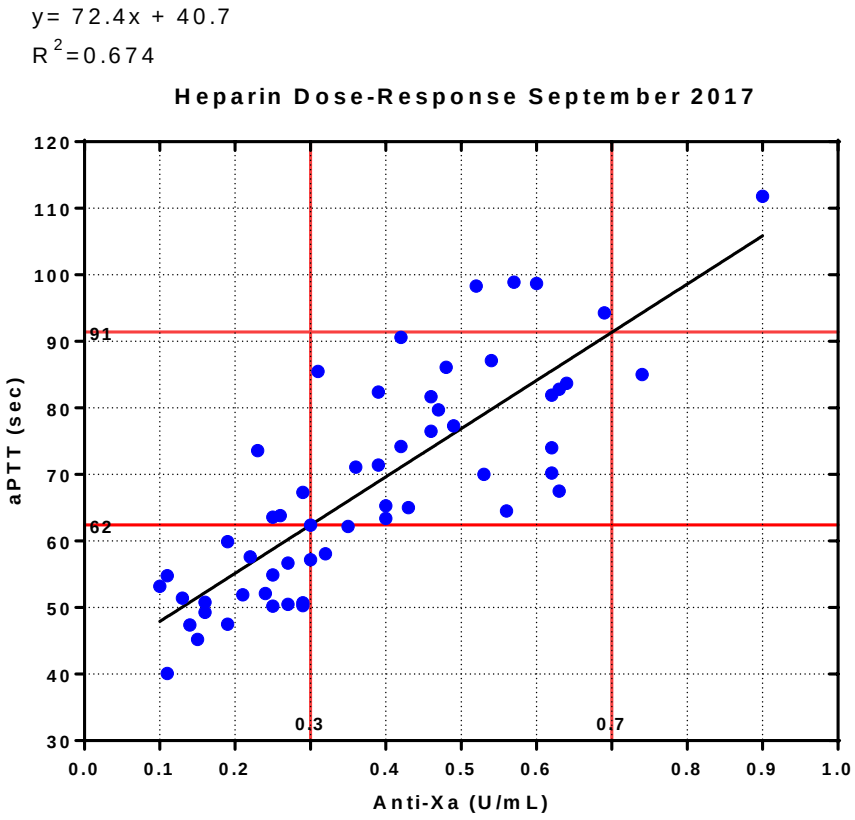
UNFRACTIONATED HEPARIN (revised 9/25/14):

The activated partial thromboplastin time (aPTT) is the test most commonly employed to monitor unfractionated heparin therapy. Rare patients, however, have a quite 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 62-91 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 0.13-0.41 anti-Xa Units/mL.

Critical Value for aPTT is > 100 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 62-91 seconds
0.3-0.5 anti-Xa units corresponds to 62-77 seconds
0.2-0.5 anti-Xa units corresponds to 55-77 seconds
50-70 seconds corresponds to 0.13-0.41 anti-Xa units

LOW MOLECULAR WEIGHT HEPARIN

(revised 1/27/10):

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 (currently being 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 (currently being sent-out to our reference laboratory)..
2. Peak steady-state plasma concentrations are typically reached approximately 1-2 hours following oral administration.
   Hurst KV et al. Vascular Health and Risk Management 2017:13 263–267

Table 3: Predicted Apixaban Steady-state Exposure and Anti-Xa Activity				
	Apix. C_{max} (ng/mL)	**Apix. C_{min} (ng/mL)**	**Apix. Anti-Xa Activity Max (IU/mL)**	**Apix. Anti-Xa Activity Min (IU/mL)**
	Median [5th, 95th Percentile]			
Prevention of VTE: elective hip or knee replacement surgery				
2.5 mg twice daily	77 [41, 146]	51 [23, 109]	1.3 [0.67, 2.4]	0.84 [0.37, 1.8]
Prevention of stroke and systemic embolism: NVAF				
2.5 mg twice daily*	123 [69, 221]	79 [34, 162]	1.8 [1.0, 3.3]	1.2 [0.51, 2.4]
5 mg twice daily	171 [91, 321]	103 [41, 230]	2.6 [1.4, 4.8]	1.5 [0.61, 3.4]
Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt)				
2.5 mg twice daily	67 [30, 153]	32 [11, 90]	1.0 [0.46, 2.5]	0.49 [0.17, 1.4]
5 mg twice daily	132 [59, 302]	63 [22, 177]	2.1 [0.91, 5.2]	1.0 [0.33, 2.9]
10 mg twice daily	251 [111, 572]	120 [41, 335]	4.2 [1.8, 10.8]	1.9 [0.64, 5.8]

* Dose adjusted population based on 2 of 3 dose reduction criteria in the ARISTOTLE study.

https://www.ema.europa.eu/documents/product-information/eliquis-epar-product-information_en.pdf

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ARGATROBAN

1. When baseline aPTT is normal, argatroban is traditionally monitored using prolongation of aPTT.
2. Argatroban infusion is is typically titrated to achieve an aPTT that is 1.5 – 2.5x the patients's baseline level. Others have advocated 1.5-3x. For an idealized patient, based on current aPTT lot on 1/24/2019, the mean normal aPTT is 29 sec and the argatroban 1.5-2.5x range would correspond to 43.5-72.5 seconds).
   A 3x aPTT prolongation would correspond to 87 seconds).

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. In this case, an alternative approach is the Dilute Thrombin Time test. When this test is ordered, results are reported as follows:
   a. Thrombin Time, in seconds
   b. The corresponding estimated plasma concentration of argatroban, obtained from a standard curve

4. We no longer provide a dervied aPTT value (expected aPTT value for those patients with normal baseline aPTT).
5. Based on our 3/2010 dTT versus aPTT study for argatroban monitoring:

	argatroban concentration (micro/mL)	dTT (sec)
1.5x aPTT prolongation	0.09	24
2.5x aPTT prolongation	0.85	63
3.0x aPTT prolongation	1.52	84

Other publications have shown the following argatroban therapeutic ranges:

- 0.4-0.8 microg/mL (Colucci G et al. J Transl Sci, 2015. Volume 1(2): 37-42)
- 0.5-1.5 microg/mL (Seidel H et al. Clinical and Applied Thrombosis/Hemostasis 2018, Vol. 24(2) 287-294)
- 0.6–1.8 microg/mL (Van Cott EM et al. Semin Thromb Hemost 2017;43:270–276)

6. When switching from a DTI to Coumadin, a Chromogenic assay for Factor X can be used to monitor the Coumadin/Warfarin effect without interference by the DTI.

BIVALIRUDIN

Bivalirudin is typically used for short-term coagulation (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 bivalirudin does need to be monitored:

1. When baseline aPTT is normal, bivalirudin can be monitored using prolongation of aPTT (typical goal is 1.5-2.5 times baseline aPTT value) (Love JE et al. Thromb Haemost. 2007. 98:234).
2. When baseline aPTT is prolonged (such as in the presence of a lupus anticoagulant), aPTT can be unreliable in bivalirudin-monitoring.

Other publications have shown the following bivalirudin therapeutic ranges:

- target 1.0 microg/mL (Colucci G et al. J Transl Sci, 2015. Volume 1(2): 37-42

3. When switching from a DTI to Coumadin, a Chromogenic assay for Factor X can be used to monitor the Coumadin/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.