Information about and Monitoring of Anticoagulant Therapy

Warfarin (Coumadin)

Indications for warfarin

- Treatment of arterial and venous thrombosis to prevent clot propagation
- Prevention of thromboembolic disease in thrombophilia, atrial fibrillation, mechanical heart valves, and high-risk surgery

Mechanism of action for warfarin

- Prevents the vitamin K dependent gamma-carboxylation of factors II, VII, IX, and X, proteins C and S, slowing thrombin production

Dosage of warfarin

- 5-10 mg/day with no loading dose. Must be monitored due to unpredictable half-life. Affected by many drugs and dietary variations.
- Requires 2-7 days to reach therapeutic levels. To achieve immediate anticoagulation, begin with heparin.

Laboratory monitoring: The INR

- PT generates the international normalized ratio (INR) by this formula:

INR = (Patient PT/MRI PT) ^{ISI} Where…

PT = prothrombin time in seconds
MRI = geometric mean of reference interval
ISI = international sensitivity index supplied by reagent manufacturer

Target INRs

- Post-myocardial infarction, most therapy and prophylaxis: INR 2.0-3.0
- Mechanical heart valves: INR 2.5-3.5

Laboratory monitoring sequence

- Daily until INR is therapeutic twice at least 24 hours apart
- Twice a week for 2 weeks, then once a month until therapy is complete

Alternative Laboratory monitoring

- Coagulation Factor X Chromogenic Activity Assay

1. Useful for: monitoring oral anticoagulant therapy (warfarin, DTIs, etc.) in patients whose plasma contains lupus anticoagulants .
2. Background: The antithrombotic effect of oral vitamin K antagonists (eg, warfarin) is mediated by reduction in the plasma activity of vitamin K-dependent procoagulant factors II (prothrombin) and X. The intensity of oral anticoagulation therapy with vitamin K antagonists must be monitored and adjusted to a narrow therapeutic range; undermedicating increases the risk of thrombosis, while overmedicating increases the risk of bleeding. Such therapy typically is monitored with the prothrombin time/international normalized ratio (INR) system.
3. Lupus anticoagulants (LAC) are autoantibodies that interfere with phospholipid-dependent clotting tests and most commonly cause prolongation of the activated partial thromboplastin time (APTT). LAC can be associated with a prothrombotic disorder termed the antiphospholipid syndrome. LAC occasionally may cause prolongation of the baseline prothrombin time, rendering the INR system inaccurate for monitoring the intensity of oral anticoagulant therapy. LAC-induced prolongation of the prothrombin time is most commonly seen with recombinant human tissue factor thromboplastins (ie, prothrombin time reagents) with a low international sensitivity index (ISI) such as Innovin (ISI = 1.0). The chromogenic factor X activity is an alternative assay for monitoring oral anticoagulant therapy. This assay is unaffected by LAC because the assay end point is not a phospholipid-dependent clotting time.
4. Interpretation: a chromogenic factor X activity of approximately 20-35% corresponds to the usual warfarin therapeutic INR = 2.0-3.0.
5. Interference: Liver disease and vitamin K deficiency may lower factor X levels.

Bleeding Risk Assessment Score for Outpatients on Warfarin

HEMORR$_2$HAGES

Gage BF, Yan Y Milligan PE, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillatiion. Am Heart J 2006; 151:713-9.

Letter	Clinical characteristic	Risk Points
H	Hepatic or renal disease	1
E	Ethanol abuse	1
M	Malignancy	1
O	Older age (>75 yrs)	1
R	Reduced platelet count or function	1
R	Rebleeding risk (that is: history of bleeding)	2
H	Hypertension, uncontrolled	1
A	Anemia	1
G	Genetic factors (CYP2C9 variant)	1
E	Excessive fall risk	1
S	Stroke	1

Risk Score	Observed outpatient risk of major bleeding (%/pt-yr)
0	1.9
1	2.5
2	5.3
3	8.4
4	10.4
>=5	12.3

Outpatient bleeding risk index

Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting major bleeding in outpatients treated with warfarin. Am J Med. 1998;105:91-9. Aspinall SL, DeSanzo BE, Trilli LE, et al. Bleeding Risk Index in an anticoagulation clinic. Assessment by indication and implications for care. J Gen Intern Med. 2005;20:1008-13.

Risk Factor	Points
Age > 65	1
Stroke history	1
GI bleeding history	1
Presence of 1 or more comorbid conditions (recent MI; SCr>1.5 mg/dL; HCT <30%; Diabetes	1

Bleeding risk group	Observed outpatient risk of major bleeding	Observed outpatient risk of minor bleeding
0 points	0.8%/pt-yr	8.5%/pt-yr
1-2 points	2.6%/pt-yr	5.3%/pt-yr
3-4 points	9.7%/pt-yr	6.1%/pt-yr

The HAS-BLED Score

Pisters R, Lane DA, Nieuwlaat R, deVos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1 year risk of major bleeding in patients with atrial fibrillation. The Euro Heart Survey. Chest 2010; 138:1093-1100

Letter	Clinical Characteristic	Definition	Risk Points
H	**HTN**	**Uncontrolled; >160 mmHg systolic**	**1**
A	**Abnormal kidney &/or liver function (1 pt each)**	**Renal: chronic dialysis, translplant, or SCr > 2** **Liver: chronic hepatic disease or lab evidence**	**1 or 2**
S	**Stroke**	**Prior history of stroke**	**1**
B	**Bleeding**	**Bleeding history, anemia, or predisposition to bleeding**	**1**
L	**Labile INRs**	**Therapeutic time-in-range <60%**	**1**
E	**Elderly**	**Age >65 years**	**1**
D	**Drugs &/or alcohol**	**Drugs: concurrent antiplatelet drugs** **Alcohol: 8 or more drinks per week**	**1 or 2**

Risk Score	Incidence of major bleeding (%/pt-yr)
0	**1.13**
1	**1.02**
2	**1.88**
3	**3.74**
4	**8.7**
5	**12.5**
6 - 9	**No patients**

Managing warfarin overdose

No bleeding	Warfarin dosage
INR 3.5-5	Decrease, do not stop drug
INR 5-8	Decrease, consider 1 mg K PO (K = Potassium; PO = Oral)
INR 5-8, bleeding risk high	Decrease, give 2.5-5 mg K PO or1 mg SC
INR > 8	Stop drug, give 2.5-5 mg K PO or 2-3 mg SC
INR > 8, bleeding risk high	1. Stop drug, give 5 mg K PO or 3-5 mg SC 2. Consider 10 mL/kg FFP or 25 U/kg PCCs (FFP = Fresh Frozen Plasma; PCC = Prothrombin Complex Concentrate)
Minor bleeding	**Warfarin dosage**
INR 2-3.5	Decrease, look for site
INR 3.5-5	Stop drug, reinstitute at lower dose
INR 5-8	Stop drug, give 2.5 mg K PO or 1 mg SC
INR 5-8, thrombotic risk high	Stop drug, do not give K
INR > 8	1. Stop drug, give 5 mg K PO or 2-5 SC 2. Consider 10 mL/kg FFP or 25 U/kg PCCs

Major bleeding	Warfarin dosage
INR 2-3.5	1. Stop drug, give 5 mg SC K or IV, repeat as necessary, look for bleeding site
INR 3.5-5	1. Stop drug, give 5-10 mg K SC or IV, repeat 2. Consider 10-15 mL/kg FFP or 25-50 U/kg PCCs
INR 5-8	1. Stop drug, give 5-10 mg K SC or IV, repeat 2. Give 15 mL/kg FFP or 25-50 U/kg PCCs
INR >8	1. Stop drug, give10 mg K SC or IV, repeat 6h 2. Give 15 mL/kg FFP or 25-50 U/kg PCCs

WARFARIN DOSING NOMOGRAM FOR MAINTENANCE THERAPY

For Goal INR 2-3	Dosing Adjustments	For Goal INR 2.5-3.5
INR < 1.5	• Consider a booster dose of 1 1⁄2 -2 times daily maintenance dose • Consider resumption of prior maintenance dose if factor causing decreased INR is transient [eg: missed warfarin dose(s)] • If dosage adjustment needed, increase maintenance dose by 10%–20%	INR < 2.0
INR 1.5 - 1.8	• Consider a booster dose of 1 1⁄2 – 2 times daily maintenance dose • Consider resumption of prior maintenance dose if factor causing decreased INR is • Considered [eg: missed warfarin dose(s)] • If dosage adjustment needed, increase maintenance dose by 5-15%	INR 2.0 – 2.3
INR 1.8 – 1.9	• No dosage adjustment may necessary if the last two INRs were in range, if there is no clear explanation for the INR to be out of range, and if in the judgment of the clinician, the INR does not represent an increased risk of thromboembolism for the patient • Consider a booster dose of 1 1⁄2 – 2 times daily maintenance dose • Consider resumption of prior maintenance dose if factor causing decreased INR is transient • [eg: missed warfarin dose(s)] • f dosage adjustment needed, increase maintenance dose by 5%–10%	INR 2.3 – 2.4
INR 2.0 – 3.0	**Desired range**	INR 2.5 – 3.5
INR 3.1 – 3.2	• No dosage adjustment may necessary if the last two INRs were in range, if there is no clear explanation for the INR to be out of range, and if in the judgment of the clinician, the INR does no represent an increased risk of hemorrhage for the patient • Consider continuation of prior maintenance dose if factor causing elevated INR is transient [eg: acute alcohol ingestion] • If dosage adjustment needed, decrease maintenance dose by 5%–10%	INR 3.6 – 3.7
INR 3.3 – 3.4	• Consider holding 1⁄2 to 1 dose • Consider resumption of prior maintenance dose if factor causing elevated INR is transient [eg: acute alcohol ingestion] • If dosage adjustment needed, decrease maintenance dose by 5%–10%	INR 3.8 – 3.9
INR 3.5 – 3.9	• Consider holding 1 dose • Consider resumption of prior maintenance dose if factor causing elevated INR is transient [eg: acute alcohol ingestion] • If dosage adjustment needed, decrease maintenance dose by 5%–15%	INR 4.0 – 4.4
INR > 4.0	• Hold until INR < upper limit of therapeutic range • Consider use of minidose PO vitamin K • Consider resumption of prior maintenance dose if factor causing elevated INR is transient [eg: acute alcohol ingestion] • If dosage adjustment needed, decrease maintenance dose by 5%–15%	INR >= 4.5

Standard Unfractionated Heparin (UFH)

Indications for UFH
- Treatment of arterial and venous thrombosis to prevent clot propagation

Mechanism of action
- Increases the inhibitory effect of antithrombin on the serine proteases thrombin, IXa, Xa, XIa, and XIIa with greatest effect upon thrombin.
- UFH clearance varies by individual and requires routine monitoring

Usual dosage
- 80 IU/kg bolus, 8 IU/kg/h IV started concurrently with warfarin
- Discontinue after 5 days if the INR has been therapeutic for at least 24 hours
- **Fixed dosing**
  1. 250 units/kg SC BID with no aPTT monitoring
- **Initial adjusted-dose SC UHF**
  1. 240 U/kg SC SID
  2. Check aPTT 6 hours after dose.
  3. Adjust to maintenance dosing per Maintenance Dosing Table below.
- **Conversion from continuous infusion UFH to adjusted dose SC UFH** -
  1. Calculate 24 hours dosing requirement to maintain aPTT, divide into two q12h doses.
  2. Discontinue IV UFH and administer first SC dose within 1 hour.
  3. Check 1st aPTT 6 hours after 1st dose
  4. Adjust to maintenance dosing per Maintenance Dosing Table below.
- **Conversion from warfarin to adjusted dose SC UFH**
  1. Discontinue warfarin.
  2. Give 240 U/kg UFH SC when INR < lower limit of therapeutic range.
  3. Check aPTT 6 hours after the 1st dose.
  4. Adjust to maintenance dosing per Maintenance Dosing Table below.

- Maintenance Dosing Table

aPTT*	q 12h Dosing Adjustment (round to nearest 500 units)	Next aPTT 6 hours after a dose every…
<40	Increase by 36-48 U/kg	1-3 days
40-59	Increase dose 24-36 U/kg	
60-100	No change	4-7 days
101-120	Decrease dose by 6-12 U/kg	1-3 days
121-140	Decrease dose by 12-24 U/kg	
>140	Decrease dose by 24-36 U/kg	

LABORATORY MONITORING OF HEPARIN THERAPY

RECOMMENDED LABORATORY TEST
Currently, the Activated Partial Thromboplastin Time (aPTT) is the laboratory test most commonly used to monitor UNFRACTIONATED HEPARIN THERAPY. However, some patients receiving heparin but not demonstrating an adequate aPTT prolongation may require further laboratory evaluation for heparin resistance. The AntiXa test can *quantitatively* determine the plasma level of Unfractionated Heparin as well as Low Molecular Weight Heparin.

aPTT THERAPEUTIC RANGE
Historically, the laboratory has recommended an aPTT prolongation of 1.5 – 2.5 times the MEAN NORMAL REFERENCE INTERVAL. (The MEAN NORMAL value is recalculated with each change in reagent lot number, approximately once per year.) The current MEAN NORMAL is reported with each patient test result.

Example: aPTT MEAN NORMAL = 30 seconds (10/16/06 to present)
Therapeutic Range = 45 – 75 seconds (1.5 – 2.5 x MEAN NORMAL)

Recently, another method of determining the Heparin Therapeutic Range was developed utilizing a procedure derived from Brill-Edwards, et al, in which aPTT values and heparin levels are obtained from patients actually receiving heparin. Using linear-regression, a graph is prepared that correlates the aPTT in seconds to the heparin Anti-Xa units. The ranges established, are the time in seconds equivalent to 0.1 to 0.3 and 0.3 to 0.7 Anti-Xa units of heparin.

Therapeutic Range =

0.1 Units =	44 seconds (aPTT)
0.3	= 63 seconds
0.7	= 101 seconds

FREQUENCY OF aPTT MONITORING

INITIATION PHASE: Upon initiation of heparin therapy, the aPTT test should be ordered every 6 hours until the result falls within the target therapeutic range. Whenever the heparin dosage is changed, the aPTT should be reevaluated every 6 hours until the desired therapeutic range is reached.

STABLE PHASE: Following attainment of a stable aPTT prolongation within the therapeutic range, the aPTT test should be ordered once a day until heparin therapy is discontinued.

SPECIMEN COLLECTION
- The daily collection time should be standardized (preferably prior to 10 AM) to avoid any diurnal variation in aPTT results (despite constant heparin infusion rates).
- To avoid falsely prolonged aPTT results due to heparin contamination, specimens for monitoring heparin therapy should not be collected from the same extremity used for heparin infusion or from an indwelling catheter

IMPORTANT NOTES:

- Prolongation of the aPTT does not necessarily indicate that the blood is effectively anticoagulated in vivo. A variety of conditions can complicate the administration and monitoring of unfractionated heparin therapy (liver disease, renal disease, obesity, aging, etc.).
- Patients receiving heparin but not demonstrating an adequate aPTT prolongation may require further laboratory evaluation for heparin resistance. Contact the laboratory for assistance (409-772-3314).
- Patients with anti-phospholipid antibodies ("lupus anticoagulants") may exhibit a significant prolongation of the aPTT yet still be at increased risk of thrombosis. Specialized assays are required for heparin monitoring in patients with anti-phospholipid antibodies [as well as contact factor (factor XII, prekallikrein, HMW kininogen) deficiencies]. Contact the laboratory for assistance.
- The aPTT is **NOT** recommended for monitoring low molecular weight heparin, danaproid or direct heparin inhibitors such as hirudin.
- Call lab for further recommendations on monitoring anticoagulation

ADDITIONAL REQUIRED MONITORING:

- Baseline: platelets, Hct, PT/INR, aPTT
- During 1st 2 weeks of UFH: plates ever 2-3 days
- Ongoing therapy: platelets, Hct every 2-4 weeks.

Laboratory monitoring: PTT

- Assay 4-6 hours after bolus dosage and every 24 hours thereafter; if dose adjustment is needed, 6 hours after changing IV infusion
- UAB target for prophylaxis: 60 - 92 s; based upon anti-Xa of 0.1 to 0.4 U/mL
- UAB target for therapy: 92 - 125 s; based upon anti-Xa of 0.4 to 0.7 U/mL
- Target PTT interval varies with reagent lot; last updated 6/9/05. Contact UAB special coagulation laboratory for current values.

Laboratory monitoring: platelet count

- Check PLT count daily to detect heparin induced thrombocytopenia (HIT)
- If count drops 30-50%, consider HIT, withdraw heparin, start alternative anticoagulant, order confirmatory test for HIT

Overdose of UFH

- Stop heparin and monitor PTT. Heparin half-life is approximately 30 minutes. If bleeding is severe, consider protamine sulfate (1 mg/100 units heparin)
- FFP does not reverse heparin effect

Heparin-induced Thrombocytopenia with Thrombosis (HIT)

From 1-5% of patients receiving unfractionated heparin develop HIT. An antibody to heparin-bound platelet factor 4 (PF4) that activates platelets causes HIT. HIT is a major source of morbidity and mortality, and must be rigorously guarded against. Daily platelet counts throughout and following heparin therapy are the primary defense. A 30-50% decrease, even when the count remains within the normal range, may signal the onset of HIT. Laboratory confirmation consists of an immunoassay for the anti-heparin-PF4 antibody. This assay requires several hours and yields a relatively high false positive rate, thus is considered confirmatory but not diagnostic. When the clinical suspicion is high, heparin should be replaced with one of the direct thrombin inhibitors Lepirudin or Argatroban, until the clinical situation is elucidated.

Low Molecular Weight Heparin (LMWH): Enoxaparin (Lovenox), Dalteparin or Tinzaparin

Indications for LMWH

- Prevention or treatment of thromboembolic disease

Half-life of Enoxaparin

- 4-5 hours (onset 3-5 hours).

Mechanism of action

- Increases the inhibitory effect of antithrombin on the serine proteases thrombin and Xa with greatest effect upon Xa
- LMWH clearance is predictable and requires little monitoring in uncomplicated thrombosis; enoxaparin accumulates in renal insufficiency

Dosage for Enoxaparin

- Prophylaxis: 40 mg SC once a day (for morbidly obese, may need 60 mg)
- Therapeutic: 1 mg/kg q12h (maximum of 150 mg)

Laboratory monitoring of Enoxaparin

- Use chromogenic anti-Xa heparin assay; PTT is insensitive
- Assay unnecessary in uncomplicated treatment situation
- Assay needed for infants, children, obese or underweight patients, or those with renal disease, long-term treatment, pregnancy, or unexpected bleeding or thrombosis
- Collect blood specimen 4 h after SC dose
- Target for prophylaxis: 0.2 to 0.4 anti-Xa U/mL
- Therapeutic target for twice-daily SC administration: 0.6-1.0 anti-Xa U/mL
- Therapeutic target for once-daily SC administration: 1.0-2.0 anti-Xa U/mL

SHORT TERM MONITORING GUIDELINES

- Baseline PT/aPTT
- Baseline hematocrit (then prn if bleeding is suspected or confirmed
- Baseline platelet count, and q2-3 days during first 2 weeks of LMWH therapy
- Baseline serum creatinine, and q7days, (then prn if change in renal function is suspected, or if bleeding is suspected or confirmed).

LONG TERM MONITORING GUIDELINES

Patient weight	q1-3 months and adjust LMWH dose if needed
Platelet count	q1-3 months
Hematocrit	q1-3 months
Serum creatinine/CrCl	q1-3 months (and PRN if change in renal function is suspected or if bleeding is suspected or confirmed) and adjust LMWH dose if needed
Trough antiXa level	• q1-3 months if CrCl > 60mL/min • q1 month if CrCl <60mL/min • goal: <0.5 unitsl/mL (adjust LMWH dose or dosing interval if needed

USE IN PREGNANCY

1st and 2nd Trimester		3rd Trimester
Patient weight	q1 month and adjust LMWH dose if needed	q2 weeks
Platelet count	q1 month	q2 weeks
Hematocrit	q1 month	q2 weeks
Serum creatinine/CrCl	q1 month and adjust LMWH dose if needed	q2 weeks and adjust LMWH dose if needed
Trough antiXa level	• q1-3 months if CrCl > 60mL/min • q1 month if CrCl <60mL/min • goal: <0.5 unitsl/mL (adjust LMWH dose or dosing interval if needed	• q1 month if CrCl > 60mL/min • q2 weeks if CrCl <60mL/min • goal: <0.5 unitsl/mL (adjust LMWH dose or dosing interval if needed
Peak antiXa level	• NA	• q2 weeks • check 4 hours after dose • goal 0.5-1 unit/mL (for q12h dosing of LMWH • Adjust LMWH dosing if needed, based on the table below

Peak antiXa Dosing Adjustments

Peak antiXa level (units/mL)	Hold next dose	Dosage change	Next antiXa Level
<0.35	No	Increase 25%	4hrs after next dose
0.35-0.49	No	Increase 10%	4hrs after next dose
0.5-1	No	None	Next day, then within 1 week
1.1-1.5	No	Decrease 20%	Before next dose
1.6-2	For 3hrs	Decrease 30%	Before next dose and 4hrs after next dose
>2	Until antiXa level <0.5	Decrease 40%	Before next dose and q12h until antiXa level <0.5 units/mL

Fondaparinux (Arixtra, pentasaccharide)

Dosage
- Prophylaxis: 2.5 mg SC once a day
- Therapeutic: Not established

Mechanism
- Selective, indirect Factor Xa inhibitor through antithrombin III. It does not have antithrombin II activity. It reversibly binds to antithrombin III, so once binding to factor Xa has occurred, it is released and catalyzes another reaction with antithrombin III leading to the inhibition of many Factor Xa molecules by one fondaparinux molecule.

Laboratory monitoring of Fondaparinux
- Use chromogenic anti-Xa heparin assay; PTT is insensitive
- Assay not necessary in uncomplicated treatment situation
- Assay needed for infants, children, obese or underweight patients, or those with renal disease, long-term treatment, pregnancy, or unexpected bleeding or thrombosis
- Collect blood specimen 4 h after a SC dose
- Pentasaccharide target: 0.14 to 0.19 mg/L.

Direct Thrombin Inhibitors (DTIs): Argatroban, Bivalirudin, Hirudin, Lepirudin and Dabigatran

DTI indications

- Substitute for heparin when HIT is suspected or confirmed. Even when HIT's only manifestation is thrombocytopenia and heparin is stopped, risk of thrombosis in subsequent 30 days approaches 50% unless alternative anticoagulant is used.
- In HIT, warfarin may be introduced when platelet count starts to increase but DTIs should be continued until platelet count normalizes. After 4-5 days of warfarin, if platelet count is normal and PT is therapeutic, stop DTI for a few hours and recheck INR. If between 2-3, it is safe to discontinue.
- Dabigatran indicated in Atrial fibrillation.

Mechanism

- Directly inhibit thrombin, even in the presence of bound fibrin. Actions are independent of antithrombin III.
- Two types:
  1. Irreversible inhibitors - Parenteral
     a. Based on Hirudin (leech spit)
     b. Synthetic analogs
        i. Lepirudin (recombinant form)
        ii. Bivalirudin (synthetic form)
  2. Reversible inhibitors - PO
     a. Argatroban (synthetic derived from L-arginine)
     b. Dabigatran

DTI dosages

- Lepirudin: 0.4 mg/kg slowly IV, then 0.15 mg/kg continuous infusion for 2-10 days depending on indication
- Argatroban: 2 µg/kg/min IV

DTI half-lives

- Lepirudin: 20 minutes
- Argatroban: 39-51 minutes

Laboratory monitoring of DTIs

- PTT is used to prevent bleeding or thrombosis
- Lepirudin: collect blood four (4) hours after initial dosage, adjust dosage to PTT 1.5-3.0 x mean of reference interval
- Argatroban: collect blood two (2) hours after initial dosage, adjust dosage to PTT 1.5-3.0 x mean of reference interval
- Dabigatran is ***not intended to be monitored*** using routine coagulation testing. There is no reversal agent or antidote.
- Bivalirudin, Dabigatran, Lepirudin all accumulate in kidney failure.
- Argatroban accumulates in liver failure
- Do not start in patients with PTT longer than 2.5 x mean of reference interval
- An alternative to aPTT or PTT is a Direct Thrombin Inhibitor Assay that uses known concentrations of highly purified human thrombin. Common assay is called "HEMOCLOT." It may be used instead of an aPTT to assess DTI therapy, it is preferred because it is more sensitive and is not affected by antiphospholipid antibodies. For measuring hirudin or any other DTI in plasma, first, the diluted tested plasma is mixed with a normal pooled human plasma (Reagent 1). Clotting is then initiated by adding a constant amount of highly purified human thrombin, in the α form (Reagent 2). The clotting time measured is directly related to the concentration of hirudin or assayed DTI in the tested plasma.
- Alternative to aPTT or PTT is a chromogenic DTI assay called "BIOPHEN DTI." This assay quantitatively measures the anti-IIa activity in patient's plasma.
- The chromogenic factor X assay is used instead of INR in patients with antiphospholipid antibodies (e.g., patients with lupus), or in patients on concurrent direct thrombin inhibitors, that might interfere with INR. See above (Warfarin monitoring).

Direct Factor Xa Inhibitor: Rivaroxaban

DFI indications

- Reduction of risk of stroke and systemic embolism in non-valvular atrial fibrillation and prophylaxis of deep vein thrombosis in patients undergoing knee or hip replacement surgery.

Mechanism

- Binds to and inhibits factor Xa without needing antithrombin III. It is specific for factor Xa with no effect on other coagulation cascade components. Small size allows them to inactivate circulating as well as bound forms of factor Xa.

DFI dosage

- 15-20 mg PO SID with evening meal

DFI half-life

- Healthy subject: 5-9 hours
- Elderly 11-13 hours
- Rivaroxaban is a CYP3A4 and pGP substrate
- Rivaroxaban is accumulated in kidney failure

Laboratory monitoring of DFI

- ***No monitoring and no antidote***

Glossary of Hemostasis terms

b-thromboglobulin	**bTG**	Oral anticoagulant therapy	**OAT**
11-dehydrothromboxane B_2	**11-DOH**	Oral contraceptive	**OCR**
Activated partial thromboplastin time	**APTT, PTT**	Percutaneous coronary intervention	**PCI**
		Peripheral artery occlusion	**PAO**
Activated protein C	**APC**	Platelet	**PLT**
Activated protein C resistance	**APCR**	Platelet factor 4	**PF4**
Acute myocardial infarction	**AMI**	Platelet -free plasma	**PFP**
Adenosine diphosphate	**ADP**	Platelet function analyzer	**PFA**
Adenosine triphosphate	**ATP**	Platelet-poor plasma	**PPP**
Anti-cardiolipin antibody	**ACA**	Plasmin-antiplasmin	**PAP**
Anti-phospholipid antibody	**APL**	Plasminogen activator inhibitor-1	**PAI-1**
Aspirin	**ASA**	Pooled normal plasma	**PNP**
Atrial fibrillation	**AFIB**	Post-transfusion purpura	**PTP**
Bernard-Soulier syndrome	**BSS**	Potassium	**K**
Cerebrovascular accident	**CVA**	Prekallikrein (Fletcher factor)	**PK**
Coronary artery bypass graft	**CABG**	Prostaglandin	**PG**
D-dimer	**D-D**	Protein C	**PC**
Deep venous thrombosis	**DVT**	Protein S	**PS**
Dilute Russell viper venom time	**DRVVT**	Proteins in vitamin K antagonism	**PIVKA**
Direct thrombin inhibitor	**DTI**	Prothrombin complex concentrate	**PCC**
Disseminated intravascular coagulation	**DIC**	Prothrombin fragment 1+2	**PF 1+2**
Ecarin clotting time	**ECT**	Prothrombin time (protime)	**PT**
Endothelial cell	**EC**	Prothrombin time ratio	**PTR**
Factor V Leiden mutation	**FVL**	Pulmonary embolism	**PE**
Fibrinogen	**Fg**	Red blood cell	**RBC**
Fibrin (ogen) degradation products	**FDP**	Russell viper venom time	**RVVT**
Fibrin (ogen) split products	**FSP**	Smooth muscle cell	**SMC**
Fibroblast	**FB**	Serine protease inhibitor	**SERPIN**
Four times a day	**QID**	Solid-phase red blood cell agglutination assay	**SPRCA**
Fresh frozen plasma	**FFP**	Staphylokinase	**SAK**
Glanzmann thrombasthenia	**GT**	Streptokinase	**SK**
Glycoprotein IIb	**GPIIb**	Subcutaneous	**SC, SQ**
Hematocrit	Hct	Three times a day	**TID**
Heparin-induced thrombocytopenia with thrombosis	**HIT, HITT**	Thrombin activated fibrinolysis inhibitor	**TAFI**
		Thrombin-antithrombin	**TAT**
High molecular weight kininogen (Fitzgerald factor)	**HMWK**	Thrombin clotting time	**TCT, TT**
Homocysteine	**HCY**	Thrombotic thrombocytopenic purpura	**TTP**
Hormone replacement therapy	**HRT**	Thrombomodulin	**TM**
Human platelet antigen	**HPA**	Thromboxane A_2	**TXA_2**
Immune (idiopathic) thrombocytopenic purpura	**ITP**	Thromboxane B_2	**TXB_2**
International normalized ratio	**INR**	Tissue factor	**TF**
International reference preparation	**IRP**	Tissue plasminogen activator	**TPA**
International sensitivity index	**ISI**	Transient ischemic attack	**TIA**
Interleukin	**IL**	Tumor necrosis factor	**TNF**
Intracranial hemorrhage	**ICH**	Twice a day	**BID**
Intramuscular	**IM**	Unfractionated (standard) heparin	**UFH**
Intravascular	**IV**	Unstable angina	**UA**
Lupus anticoagulant	**LA, LAC**	Urokinase	**UK**
Low molecular weight heparin	**LMWH**	Venous thromboembolism	**VTE**
Neonatal alloimmune thrombocytopenic purpura	**NAIT**	von Willebrand disease	**vWD**
Normal plasma	**NP**	von Willebrand factor	**vWF**
Once a day	**SID**	White blood cell	**WBC**

References:

1. University of Alabama, Birmingham, Department of Pathology http://peir.path.uab.edu/coag/article_221.shtml
2. University of Texas Medical Department www.utmb.edu/lsg/hem/HEPARIN_THERAPY.htm
3. University of Washington Department of Medicine Pharmacy Services - http://uwmcacc.org/lmwh.html