Introduction and review of Anticoagulant drugs

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www.pchd.sbmu.ac.ir

28-5-95

Refferences :

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- **Therapeutic advances in thrombosis / edited by David J. Moliterno ... [et al.]. – 2nd ed./2013**
- **Katherine Harter,Michael Levine,Sean O. Henderson; Anticoagulation Drug Therapy: A Review ; Western Journal *of* Emergency Medicine; Volume XVI, NO. 1 : January 2015**
- **SickKids Handbook of pediatric Thrombosis and Hemostasis/Victor S. Blanchette,et al-1st ed./2013**

Overview & Categories

- Anticoagulants:
  - Heparin
    - **Unfractionated Heparin**
    - **Low Molecular Weight Heparin**: **Dalteparin ; Enoxaparin ; Tinzaparin**
  - Vitamin K Antagonists : Warfarin ; Acenocoumoral ; Phenprocoumon
  - Factor Xa Inhibitors: Fondaparinux ; Rivaroxabane ; Apixaban
  - Direct Thrombin Inhibitors (DTI) : Argatroban ;Bivalirubin ; Dabigatran
- Antiaggregants:
  - COX inhibitors : ASA
  - Platelet ADP P2Y12 inhibitors:
    - Ticlopidine ; Clopidogrel; Prasugrel
    - Ticagrelor; Cangrelor; Elinogrel
  - Cyclic nucleotide phosphodiesterases (PDEs) Inhibitors : Dipiridamol
  - Protease Activated Receptor-1 (PAR) antagonists: Atopaxar; Vorapaxar
  - GP IIb-IIIa inhibitors:Abciximab,Tirofiban, and Epfitibatide
- Thrombolytic OR Fibrinolytic agents:
  - Streptokinase
  - Urokinase
  - Recombinant Tissue Plasminogen Activators:
    - Unmodified: Alteplase
    - Modified :Retplase , Tenecteplase

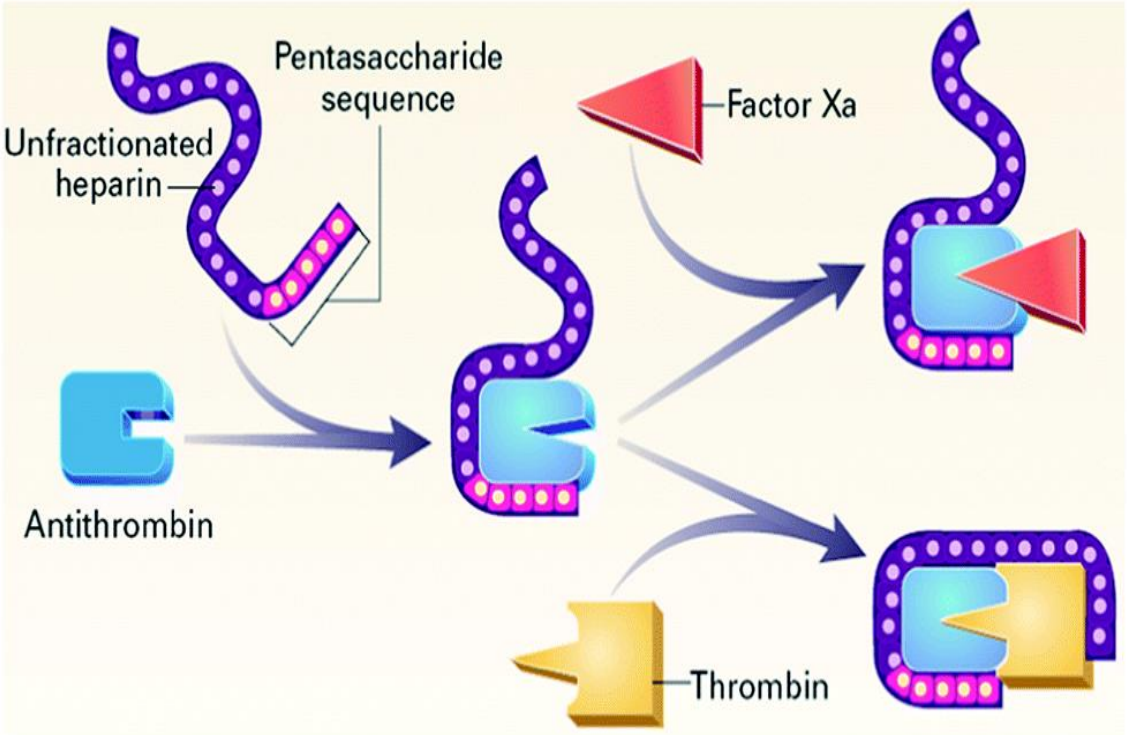
Ideal Anticoagulant

- Wide therapeutic window
- Predictable /linear dose-response curve
- Monitoring test
- Less or no need for monitoring
- Reversal of effects : immediate ; Antidote
- Organ-independent metabolism and clearance
- Rapid onset (time to maximum effect)
- T1/2 :
  - Short for acute treatment aims , especially critical situation and invasive procedures
  - Long for prophylaxis
- Oral
- Available
- Cost

HEPARIN

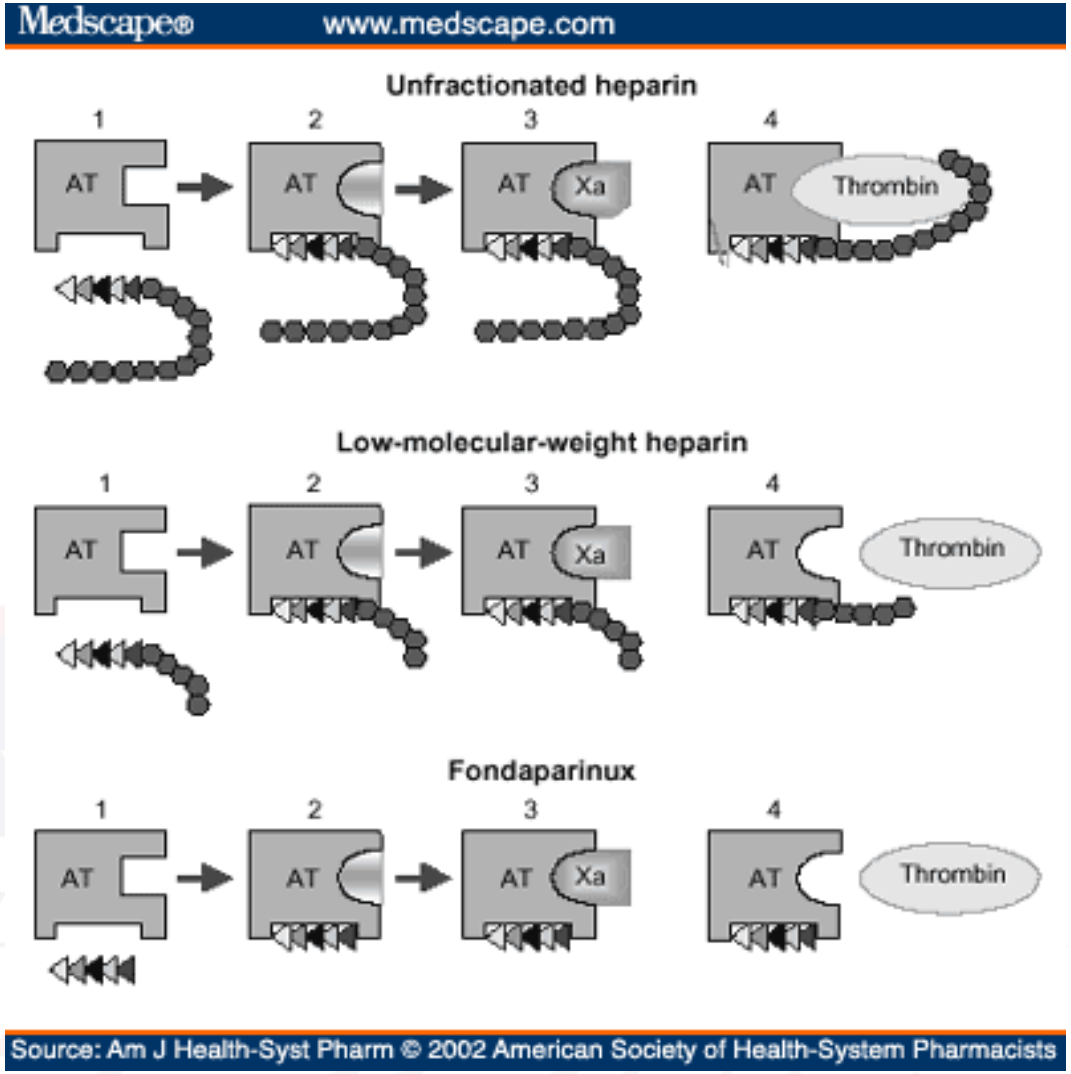
Mechanism

- **Indirectly inhibits thrombin by complexing with ATIII** (a natural inhibitor of thrombin), factor Xa, and other serine proteases to a lesser extent (e.g., factors IIa, IXa, XIa, and XIIa)
- AT III has a binding site for **pentasaccharide part** of heparins
- Active site of heparin consisted of at least **18 saccharide** units in length, increases AT III activity against II a at least 1000-fold following interaction

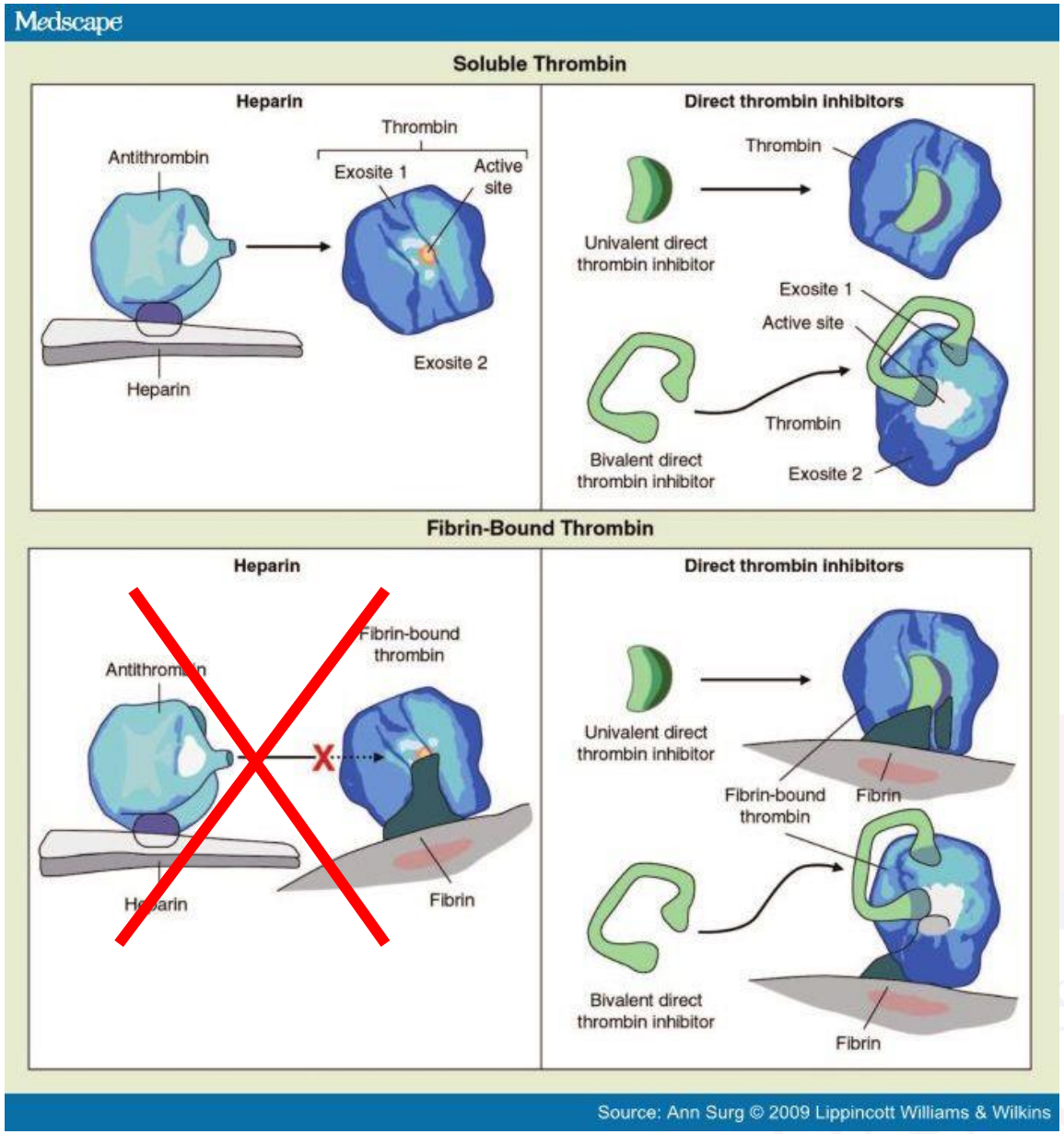


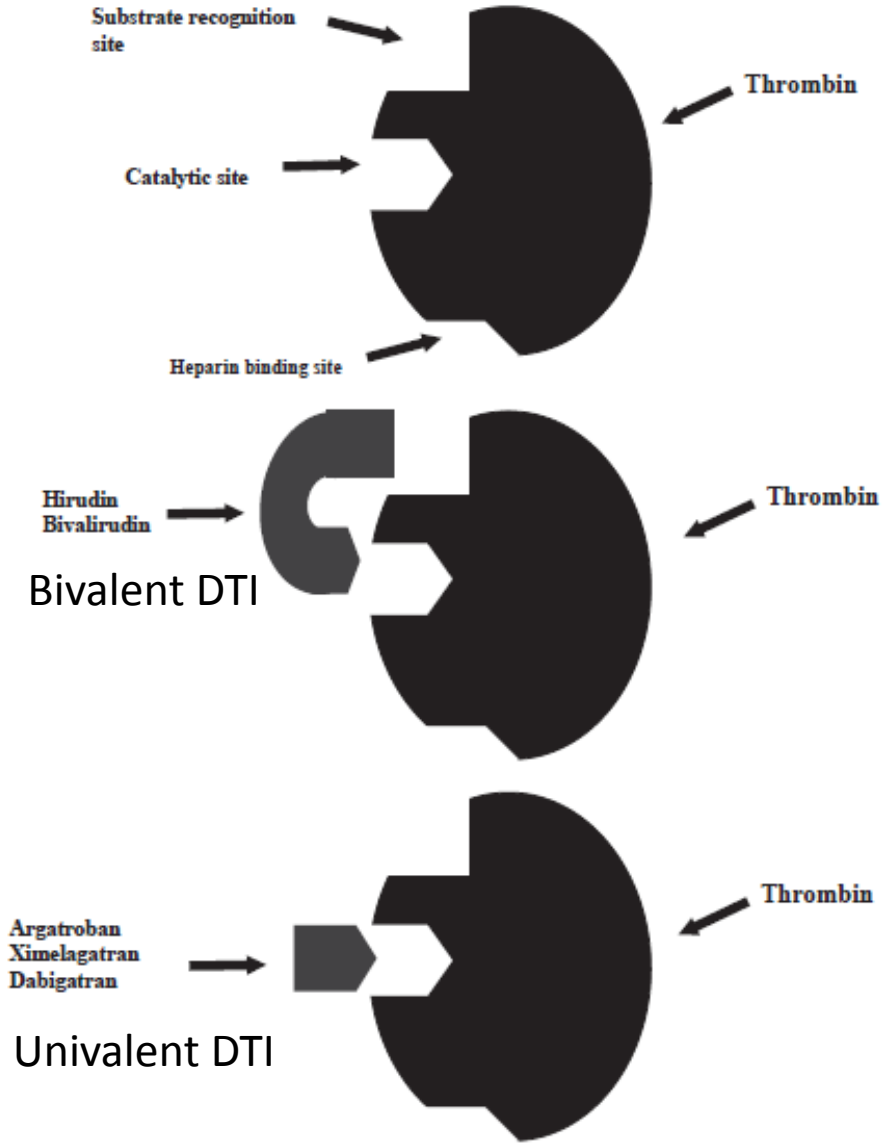
Mechanism

- Factor Xa inhibition by the heparin-ATIII complex does not require the 18-saccharide complex active binding site of heparin to AT III
  - common in UFH: inhibition at Xa and IIa in a 1:1 ratio
  - uncommon in LMWH products: inhibition at Xa and IIa in a 3:1 ratio
  - Totally absent in the pentasaccharides: inhibits directly FXa



the smaller molecules are unable to form the requisite ternary complex with IIa


Medscape
Soluble Thrombin
Heparin
Thrombin
Antithrombin
Exosite 1
Active site
Exosite 2
Heparin
Direct thrombin inhibitors
Thrombin
Univalent direct thrombin inhibitor
Exosite 1
Active site
Thrombin
Bivalent direct thrombin inhibitor
Exosite 2
Fibrin-Bound Thrombin
Heparin
Fibrin-bound thrombin
Fibrin
Direct thrombin inhibitors
Univalent direct thrombin inhibitor
Fibrin-bound thrombin
Fibrin
Bivalent direct thrombin inhibitor
Fibrin
Source: Ann Surg © 2009 Lippincott Williams & Wilkins


Substrate recognition site
Thrombin
Catalytic site
Heparin binding site
Hirudin
Bivalirudin
Thrombin
Bivalent DTI
Argatroban
Ximelagatran
Dabigatran
Thrombin
Univalent DTI

Pharmacology

- Therapeutic efficacy :
  - IV: immediately
  - SC: within 20-60 minutes
- Does not require dosage adjustment in renal failure
- Half life: 1-2 Hr
- Does not cross the placenta

Administration and Monitoring

- Benefits:
  - Nearly **immediate** anticoagulant effect
  - An ability to **monitor treatment directly using aPTT**
    - between **1.5 and 2.5 times** the normal reference value.
    - should be measured before therapy and every **4 to 6 hours** thereafter, especially with any change in dose.
      - Consider heparin contamination during sampling due to at least **8 cc** dead space of peripheral catheters and more in CVLs.
- Limitations:
  - **Narrow** therapeutic window,
  - **Unpredictable** dose-response relationships,
  - Reduced ability for heparin to inhibit thrombin and factor Xa already **enmeshed in thrombus**

Intravenous Unfractionated Heparin Dosing Nomograms

FIXED-DOSE NOMOGRAM*[70]

PTT (sec)†	Bolus Doses (U)	Stop Infusion (min)	Change in Infusion‡	Time of Repeat PTT
<50	5000	0	+3 mL/hr	6 hr
50-59	0	0	+3 mL/hr	6 hr
60-85	0	0	0	Next morning
86-95	0	0	−2 mL/hr	Next morning
96-120	0	30	−2 mL/hr	6 hr
>120	0	60	−4 mL/hr	6 hr

WEIGHT-BASED NOMOGRAM[69]

Initial dose is 80 U/kg given as a bolus, followed by an infusion of 18 U/kg/hr. Dose adjustments are based on PTT values obtained every 6 hr.

PTT (sec)§	Bolus (U/kg)	Infusion (U/kg/hr)
<35	80	Increase rate by 4
35-45	40	Increase rate by 2
46-70	0	No change
71-90	0	Decrease rate by 2
>90	0	Decrease rate by 3

*Modifications occurred after initial heparin load and maintenance infusion.
†Reference range, 35-37 sec; therapeutic range, 60-85 sec (corresponds to a plasma heparin level of 0.3-0.7 U/mL anti-Xa activity).
‡1 mL/hr is approximately 40 U/hr.
§Reference range, 20-30 sec.
PTT, Partial thromboplastin time.

Box 26-3 CLINICAL SITUATIONS IN WHICH MEASUREMENT OF HEPARIN LEVELS BY ANTI–FACTOR Xa ASSAY IS APPROPRIATE

- Patients may have a prolonged PTT before heparin therapy (e.g., inherited factor deficiencies, hepatic insufficiency, APLS). Monitoring heparin dosage using the PTT in these situations is imprecise. Measurement of anti–factor Xa levels can help ensure maintenance of heparin in the proper therapeutic range.
- Patients may require anticoagulation for an acute thrombotic event or bridging for high-risk conditions (e.g., mechanical heart valves) but also have an increased risk of bleeding for various reasons (e.g., recent surgery, stroke, severe thrombocytopenia). Measurement of anti–factor Xa levels can allow for sufficient therapeutic effect without unnecessary overanticoagulation.
- Patients requiring excessively large dosages of UFH (e.g., massive acute thrombosis) will occasionally develop heparin resistance and require increasing amounts to maintain the same PTT. Following anti–factor Xa levels (range, 0.3-0.7 U/mL) can provide clinical reassurance.
- Following anti–factor Xa levels can be helpful when either LMWH or fondaparinux is used in the above clinical situations. Measuring levels may be of particular help in a patient for whom dosing accuracy is uncertain (e.g., morbidly obese patient, children, patient with renal insufficiency), or when bleeding events occur while the patient is receiving what is thought to be an appropriate dose.

APLS, Antiphospholipid syndrome; *LMWH,* low molecular weight heparin; *PTT,* partial thromboplastin time; *UFH,* unfractionated heparin.

Target Anti-Xa activity :0.3 to 0.7 U/ mL

HEPARIN RESISTANCE

- *Definition:*
  - Inadequate prolongation of the partial thromboplastin time (PTT) or activated clotting time despite administration of therapeutic dosages of unfractionated heparin (**UFH; e.g., >1500 U/hr** for the treatment of venous thromboembolism [VTE]; **400 U/kg** during cardiopulmonary bypass
- *Causes:*
  - Supraphysiologic levels of factor **VIII and/or fibrinogen (e.g., acute phase response**)
  - **Antithrombin III (ATIII) deficiency**: primary OR secondary (DIC , extensive thrombosis, CABG)
  - increased levels of **binding proteins**;
  - **Increased clearance** (e.g., during pregnancy).
- *Management:*
  - If **ATIII level is low** (e.g., <70% of normal): consider administering of FFP or an ATIII infusion to boost levels above 100%.
  - If ATIII level is normal : monitor heparin therapy with regular assay of a**nti–factor Xa levels.**

Indications:

- **Acute** VTE management : at least for the **first 5 days** ; **as effective and safe as LMWH**

Vardi M, Zittan E, Bitterman H: Subcutaneous unfractionated heparin for the initial treatment of venous thromboembolism. Cochrane Database Syst Rev (4):CD006771, 2009.

- Treatment of ACS, as an **adjunct to thrombolysis**,
- Prevention of acute vessel reocclusion in patients undergoing percutaneous coronary intervention (PCI)
- **Intraoperatively** :
  - Vascular surgery to preserve vessel patency
  - CABG to maintain extracorporeal circuits
  - Hemodialysis.
- Whom LMWH is contraindicated
- **Pregnancy**: not crossing placenta ;short half life
- Rapid & Short term Anticoagulation effect
- Critical clinical situation and need to invasive interventions
- **Renal failure and dialysis**

Side Effects and Reversal Agents

- Bleeding:
  - Major bleeding **during treatment** in approximately **3%** of those receiving therapeutic doses
  - Management :
    - Is the bleeding due to heparin?
      - Underlying & predisposition causes
    - Are there aggravating factors?
      - Other medicines and products
    - Is the concentration too high?
      - Considering time , dosage, half life of heparin:
        1. Discontinue UH
        2. **Exceptionally** reverse with protamine : 1mg for 100 units of UFH received in last 2 Hr, no more than 50 mg (* **consider allergic reaction** especially to patients with fish Allery ,or allergy to Insulin)
        3. **Do not** administer fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC).
    - Do the benefits of continuing heparin outweigh the risks?

Side Effects and Reversal Agents

- HIT:
  - Antibodies against a complex of heparin and platelet factor 4 (PF4) and are platelet activating, which leads to both thrombocytopenia and potential arterial and venous thrombosis
  - After 5-10 days ; faster in cases with Hx of heparin usage
  - Risk of HIT:
    - >1 week of treatment,
    - more frequently with UFH than with LMWH
    - postsurgical patients
    - Women
  - Management in case of **clinical suspicious** clinical suspicion
    1. **Discontinue** UH or LMWH immediately,
    2. **Send** the patient's plasma for confirmatory testing,
    3. **Start** an alternative anticoagulant (e.g., DTIs, factor Xa inhibitors, fondaparinux)
- Osteopenia:
  - Long-term (eg. Pregnancy)
  - Not completely reversible

LOW MOLECULAR WEIGHT HEPARIN

TABLE 26-5 Comparison of Heparin, Low Molecular Weight Heparin, and Fondaparinux

	Heparin	LMWH	Fondaparinux
Bioavailability with subcutaneous administration	Dose dependent, variable or low	High	High
Plasma half-life	1-2 hr	3-5 hr	17 hr
Need for monitoring	Routine (PTT > anti–factor Xa)	Occasional (anti–factor Xa)	Unlikely (anti–factor Xa)
Cost	Negligible	Moderate	Moderate
PTT prolongation	Dose dependent	Minimal, variable	Minimal or none

LMWH, Low molecular weight heparin; *PTT*, partial thromboplastin time.

- much more convenient for outpatient management
  - much more **predictable** absorption, bioavailability, and overall anticoagulant effect
  - Less monitoring need
  - Longer half life
- Anti–factor Xa levels typically reach their peak **5 hours** after the dose
- Dose modification should be considered once patients have stage 4 or 5 chronic kidney disease (CrCl of <30 mL/min) especially in Enoxaparin (in comparison to dalteparin and tinzaparin)
- No clinical significant difference between LMWH products

Administration and Monitoring

TABLE 26-6 Treatment Regimens for Low Molecular Weight Heparins

	Drug	Regimen
PROPHYLAXIS		
General surgery		
Low risk	Dalteparin (Fragmin)	2500 U, 1-2 hr preop then daily
	Enoxaparin (Lovenox)	20 mg, 1-2 hr preop then daily
	Tinzaparin (Innohep)	3500 U, 1-2 hr preop then daily
High risk	Dalteparin	5000 U, 10-12 hr preop then daily
	Enoxaparin	40 mg, 10-12 hr preop then daily
Orthopedic surgery	Dalteparin	5000 U, 8-12 hr preop then daily
	Enoxaparin	30 mg q12h starting 12-24 hr postop, or 40 mg daily starting 12 hr preop
	Tinzaparin	50 U/kg, 2 hr preop then daily; or 75 U/kg daily starting 12-24 hr postop
Spinal surgery	Enoxaparin	30 mg q12h
Multiple trauma	Enoxaparin	30 mg q12h
Medical patients	Dalteparin	5000 U daily
	Enoxaparin	20 mg daily (40 mg daily in higher-risk patients)
TREATMENT		
VTE	Dalteparin	100 U/kg q12h, or 200 U/kg daily
	Enoxaparin	1 mg/kg q12h, or 1.5 mg/kg daily
	Tinzaparin	175 U/kg daily
UA	Dalteparin	100 U/kg q12h
	Enoxaparin	1 mg/kg q12h

postop, Postoperatively; *preop*, preoperatively; *UA*, unstable angina; *VTE*, venous thromboembolism.

- **Fixed doses are typically used for thromboprophylaxis, whereas therapeutic doses are weight adjusted.**
- 1 mg of Enoxaparin is equivalent to 100 U of anti–factor Xa activity
- **Dalteparin** seems not bioaccumulated when used at **<u>prophylactic doses</u>**, even in patients with **end-stage renal disease.**[1]

Monitoring

- The target anti–factor Xa level (few data to support the clinical utility) :
  - twice-daily enoxaparin and nadroparin = 0.6 to 1.0 U/mL.
  - once-daily dosing = more than 1.0 U/mL for enoxaparin, 0.85 U/mL for tinzaparin,1.3 U/mL for nadroparin, and 1.05 U/mL for dalteparin.
- Measured 4 hours after injection
- Indicated close observation in :
  - Renal insufficiency
  - Obese individuals
  - Pediatric patients
  - Pregnant women
  - Trousseau syndrome

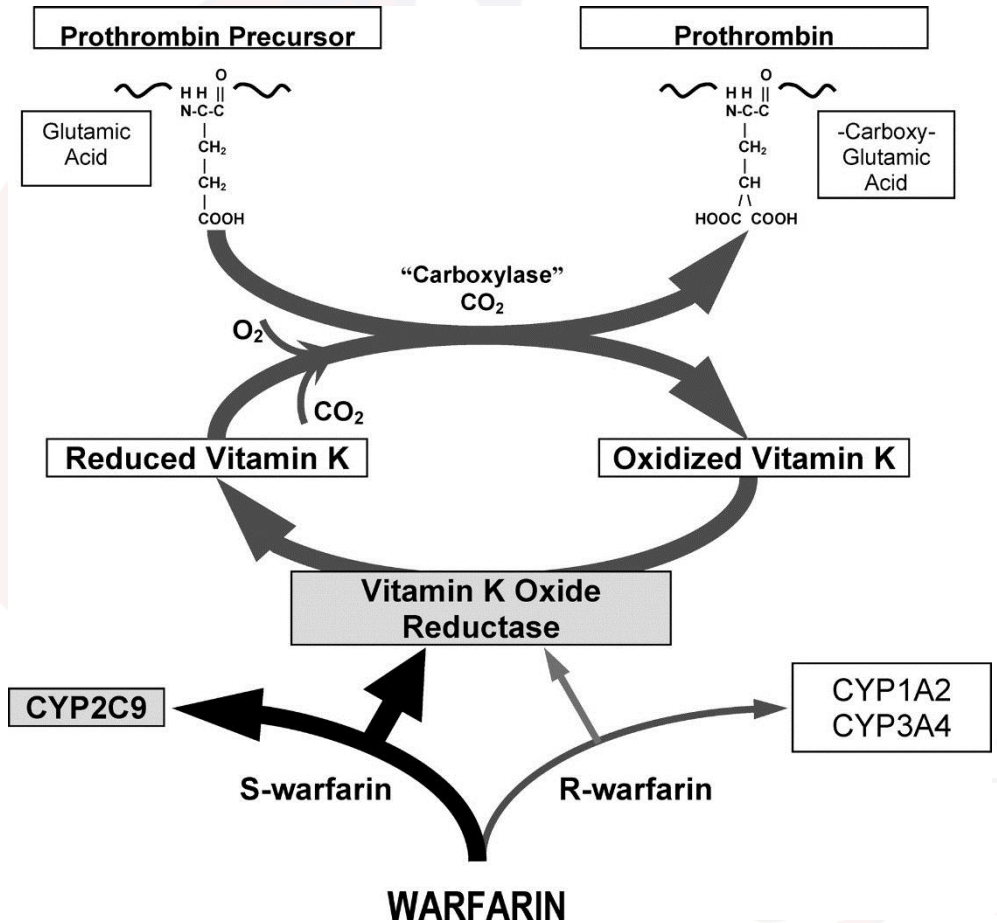
Adverse Effects

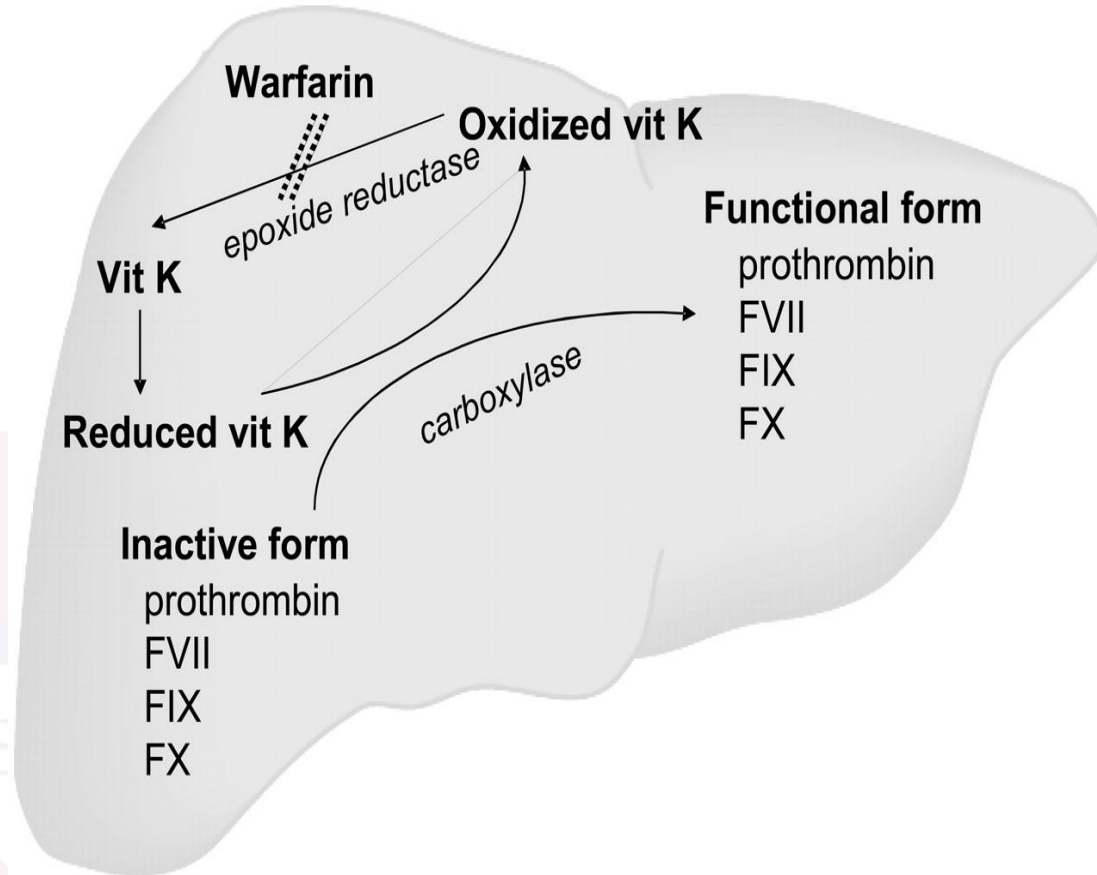
- Bleeding:
  - LMWH vs UFH : less frequent at prophylactic levels (3.9% versus 5.4%), but equivalent or higher rates with therapeutic dosing (7.9% versus 5.3%)
- HIT:
  - Less frequent than UFH , but cross reactivity is frequent and should be considered
- osteoporosis :
  - lower with LMWH than with UFH.
  - Prophylactic LMWH therapy in pregnant patients does not seem to produce any additional osteopenic effect beyond the normal physiologic pregnancy-related bone loss observed.

Reversal of Effect

- No specific antidote
- Protamine is not predictable: The main effect comes via neutralization of anti–factor IIa activity, with only partial reversal of anti–factor Xa activity
- Dosage :
  - 1 mg of protamine for every 100 U of anti–factor Xa activity delivered over the previous 8 hours
  - Second dose :0.5per 100 U of anti–factor Xa activity

VITAMIN K ANTAGONISTS


Prothrombin Precursor
Prothrombin
Glutamic Acid
-Carboxy-Glutamic Acid
"Carboxylase"
CO_2
O_2
CO_2
Reduced Vitamin K
Oxidized Vitamin K
Vitamin K Oxide Reductase
CYP2C9
CYP1A2
CYP3A4
S-warfarin
R-warfarin
WARFARIN


Warfarin
Oxidized vit K
epoxide reductase
Vit K
Functional form
prothrombin
FVII
FIX
FX
Reduced vit K
carboxylase
Inactive form
prothrombin
FVII
FIX
FX

Introduction & Pharmacology

- Coumarin since 1940 ;Warfarin since 1954
- Approximately 1% to 2% of adults in the developed world are taking warfarin or another VKA, such as acenocoumarol or phenprocoumon

Vigue B: Bench-to-bedside review: optimizing emergency reversal of vitamin K antagonists in severe haemorrhage—from theory to practice. Crit Care 13:209, 2009

- The **bioavailability** of warfarin is nearly 100%.
- However it has poor **dose-response curve**:
  - highly protein bound
  - Hepatic metabolism via the CYP450 system: Single nucleotide polymorphisms in *CYP2C9* and *VKORC1*
    - a novel personalized prediction tool for warfarin initiation found **no influence** of *CYP2C9* or *VKORC1* genotypes on **time to stable** anticoagulation or **time in the therapeutic range***(Gong IY., et al. Blood 118: 3163–3171, 2011.)*
  - dietary intake of vitamin K–containing foods

Monitoring

- **The initial rise in INR** reflects only the decreased activity of **factor VII** because it has the shortest half-life (approximately 6 hours).
- Proper anticoagulation with warfarin requires reduction in the levels of all coagulation proteins, including prothrombin, which has a plasma half-life of approximately **72 hours**
- Most individuals achieve a therapeutic INR within **4 to 7 days**
- **loading doses is not advisable**, because higher initial dose :
  - will not necessarily expedite achievement of a therapeutic INR.
  - predispose the patient to
    - **bleeding** complications to excessive factor VII depletion
    - conversely, it may create a **hypercoagulable state** from the early, rapid reduction of protein C
- Optimal dosing of warfarin must still be individualized, and there is no maximum dose
- standard INR target **of 2.0 to 3.0** for all indications except Cardiac valve replacement (mechanical) with higher INR of 2.5-3.5
- Frequent monitoring (**at least every other day**) at the start of therapy till dose stability
- "**Warfarin resistance**" : require dosing much higher than is standard (**fivefold to twentyfold)**
- Time in the therapeutic range (measured in percent): **44% to 78%,**

Indications

- Thromborophylaxis in patients with AF
- Treatment of DVT & PE
- Secondary prevention of VTE after an initial episode of DVT or PE
- Thromboprpophylaxis for :
  - Cardiac valve replacement (tissue)
  - Cardiac valve replacement (mechanical)
  - Acute myocardial infarction (MI)

HINTS FOR THE SUCCESSFUL LONG-TERM USE OF WARFARIN

- **Do not needlessly start and stop therapy:**
  - Low therapeutic INR (i.e**., 2.0-2.2**) should not result in excessive bleeding with minor procedures (e.g., biopsies, dental work).
  - Slightly supratherapeutic or subtherapeutic levels (e.g., **1.8 or 3.3**) are common (more than 25% of patients) and should not be cause for large dose alteration.
  - Significant changes in the INR (e.g., INR of **<1.5 or >6.0**) are usually explained by missed or extra doses, intercurrent illness, dietary changes, and/or new medications (e.g., antibiotics).
- Adjustments to daily dose should be small (i.e., **only ±10%-15%)** to maintain control.
- Dosing of warfarin should be viewed in terms of a cumulative **weekly quantity** :Holding warfarin for 1 day represents an approximate 14% change in weekly dose.
- After dose changes, wait for **4-7 days** before repeating the INR to ensure achievement of a new steady state.

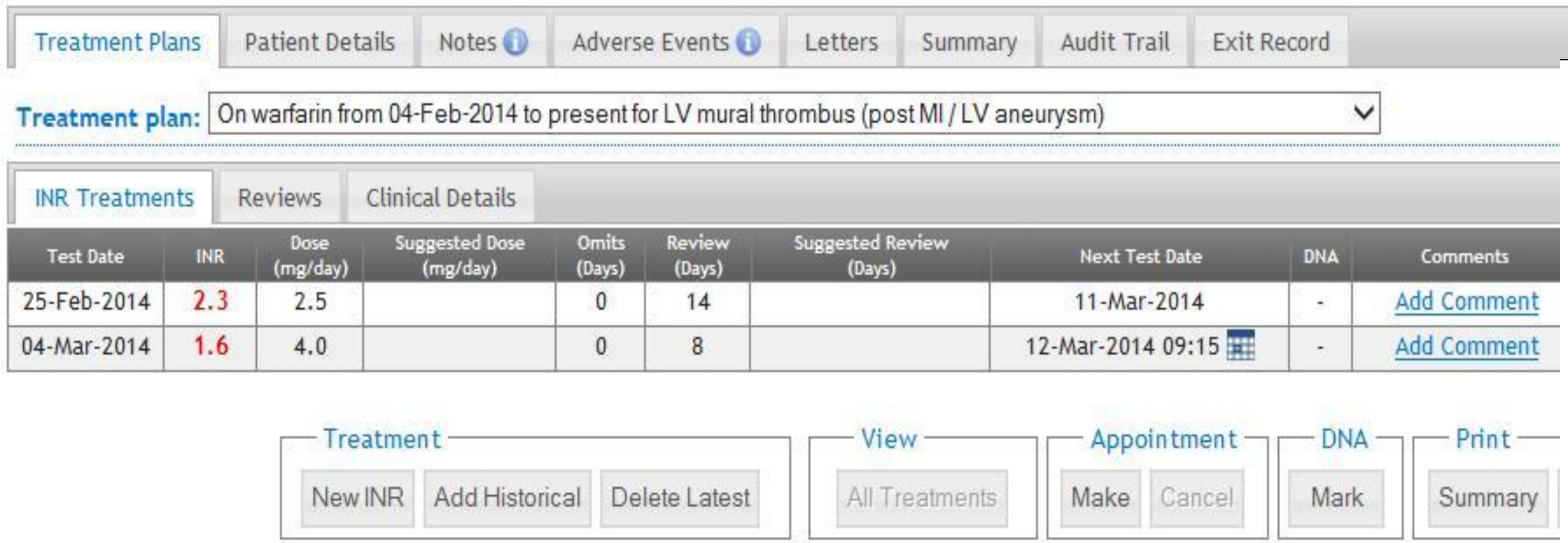
HINTS FOR THE SUCCESSFUL LONG-TERM USE OF WARFARIN

- **Specialized warfarin clinics**, run by physicians and/ or pharmacists:
  - Warfarin Diary: recorded regular INR values, as well any changes to medications, diet, or lifestyle in general
  - Warfarin Apps
  - Communication via the phone or electronically.
  - Patients can also be given a supply of vitamin K that can be taken with instruction in case of excessive INR elevation.
- **In case of any change** in daily meals , start or stop any new prescription,over-the-counter medication, or alternative medicine
  - First informing the health care team.
  - INR should be rechecked after **4 or 5 days** to assess for potential interactions.

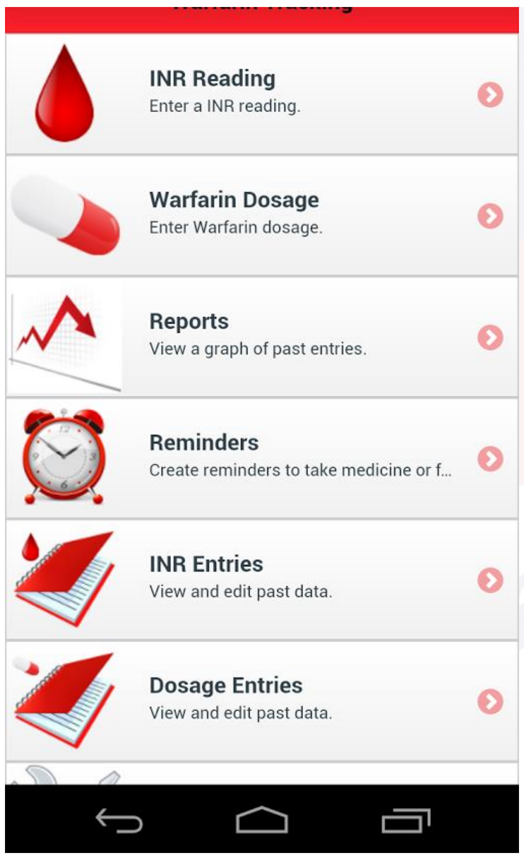
TABLE 39-7 Commonly Used Bleeding Risk Indices to Assess Risk of Bleeding in Patients Receiving Vitamin K Antagonists

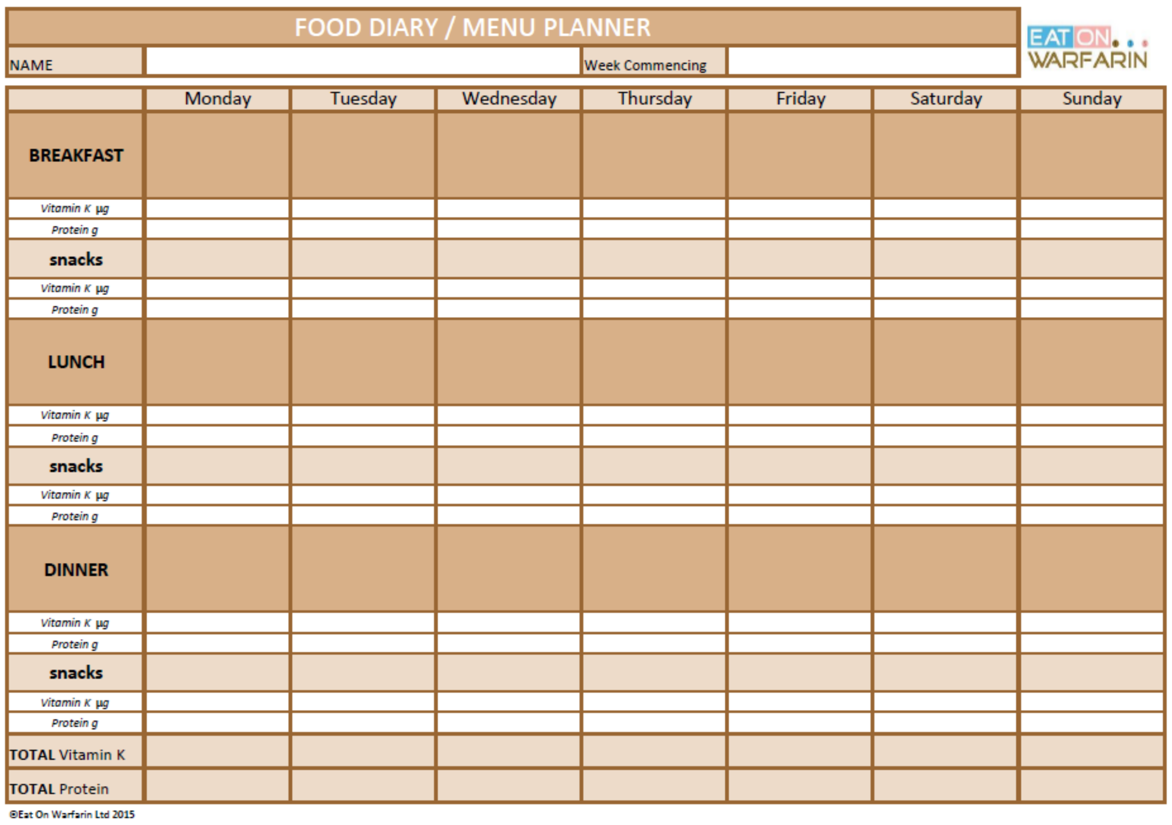
OBI		HEMORR$_2$HAGES		HAS-BLED		ATRIA	
Age ≥ 65 yr	1	Abnormal renal/liver function	1	Hypertension	1	Anemia	3
Prior stroke	1	Alcohol abuse	1	Abnormal renal/liver function	1/2	Severe renal disease	3
Prior gastrointestinal bleeding	1	Cancer	1	Stroke	1	Age ≥ 75 yr	2
Recent myocardial infarction, diabetes, hematocrit < 30%, or creatinine > 1.5 mg/dL	1-4	Age > 75	1	Bleeding	1	Any prior bleed	1
		Reduced platelet count or function	1	Labile INR	1	Hypertension	1
		Rebleeding risk	1	Elderly (>65 yr)	1		
		Hypertension	1	Drugs or alcohol	½		
		Anemia	1				
		Genetic factors	1				
		Fall risk	1				
		Stroke	1				
Low risk	0		≤1		<3		<4
High risk	≥3		≥3		≥3		≥4

INR, International normalized ratio; *OBI*, outpatient bleeding risk index.


Treatment Plans
Patient Details
Notes
Adverse Events
Letters
Summary
Audit Trail
Exit Record
Treatment plan: On warfarin from 04-Feb-2014 to present for LV mural thrombus (post MI / LV aneurysm)
INR Treatments
Reviews
Clinical Details
Test Date | INR | Dose (mg/day) | Suggested Dose (mg/day) | Omits (Days) | Review (Days) | Suggested Review (Days) | Next Test Date | DNA | Comments
25-Feb-2014 | 2.3 | 2.5 | | 0 | 14 | | 11-Mar-2014 | - | Add Comment
04-Mar-2014 | 1.6 | 4.0 | | 0 | 8 | | 12-Mar-2014 09:15 | - | Add Comment
Treatment: New INR, Add Historical, Delete Latest
View: All Treatments
Appointment: Make, Cancel
DNA: Mark
Print: Summary


DAILY INR RECORD
EAT ON WARFARIN
NAME
INR RANGE
TO
WARFARIN DOSAGE (mg)
Start Date
MON
TUE
WED
THU
FRI
SAT
SUN
Date
Day
Dose mg
Taken ✓
Notes
E.G. INR RESULTS, BLOODS TAKEN, APPOINTMENTS, SYMPTOMS


INR Reading
Enter a INR reading.
Warfarin Dosage
Enter Warfarin dosage.
Reports
View a graph of past entries.
Reminders
Create reminders to take medicine or f...
INR Entries
View and edit past data.
Dosage Entries
View and edit past data.


FOOD DIARY / MENU PLANNER
EAT ON WARFARIN
NAME
Week Commencing
Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday
BREAKFAST
Vitamin K µg
Protein g
snacks
LUNCH
DINNER
TOTAL Vitamin K
TOTAL Protein
©Eat On Warfarin Ltd 2015

Adverse Effects

- *Bleeding:*
  - 3% to 5% per year.
  - **Personalized risk estimates**:
    - Outpatient Bleeding Risk Index
    - HEMORR2HAGES score *Gage BF> ,et al. Am Heart J 151:713–719, 2006.*
  - Bleeding risk doubles for every 1-point increase in **INR above 3.0** and increases significantly above an INR of 4.5
  - **Fatality rate** of warfarin-associated bleeding is up to 15%, **more than** the day-over-day risk of thrombosis, even in very high-risk patients:
    - interruption of warfarin until the risk of bleeding is substantially reduced
  - **PO vs SC Vitamin K** :
    - SC should never be given subcutaneously, because its effects are variable and unpredictable.

Management of Various Scenarios in Patients with Warfarin-Associated Coagulopathy

modified from Patriquin C, Crowther M: Treatment of warfarin-associated coagulopathy with vitamin K. Expert Rev Hematol *4:657–667, 2011.*

Clinical Scenarios		Management Strategy
Difficult-to-control INR		**1. Question about and control for common causes of INR variability.** **2. Consider low-dose daily vitamin K supplementation**
THE NONBLEEDING PATIENT	**INR 3.0-4.5**	**1. Warfarin withdrawal 1-2 days ± weekly dose adjustment.** **2. Consider preoperative vitamin K 1 mg PO if INR elevated the day before surgery and recheck INR on day of operation.**
	INR 4.5-10	**1. Warfarin withdrawal 1-2 days ± weekly dose adjustment.** **2. Vitamin K 1 mg PO (or 0.5 mg IV).** **3. Close monitoring for INR and signs of bleeding.**
	INR >10	**1. Warfarin withdrawal ± dose adjustment.** **2. Vitamin K 2.0-2.5 mg PO (or 0.5-1.0 mg IV).** **3. Close monitoring for INR and signs of bleeding.** **4. in the absence of other risk factors necessitating hospital admission, these patients can be safely managed as outpatients.**
THE BLEEDING PATIENT	**Minor bleeding**	**1. Warfarin withdrawal ± dose adjustment.** **2. Correct the underlying defect (e.g., compression, packing, topical antifibrinolytics).** **3. Vitamin K 2.5-5.0 mg PO, with possible repeat dose after 24 hr if incomplete correction.**
	Major bleeding	**1. Warfarin withdrawal ± dose adjustment.** **2. Correct the underlying defect (e.g., compression, packing, topical antifibrinolytics).** **3. Factor replacement with prothrombin complex concentrate or fresh frozen plasma.** **4. Vitamin K 10 mg IV via slow infusion.**

PERIOPERATIVE MANAGEMENT OF WARFARIN ANTICOAGULATION

Risk of thrombotic recurrence:	Management
Low	• Hold warfarin for 4-5 days preoperatively. • Check the INR the day before surgery. Surgery can be performed if the INR is below 1.5. • Warfarin can be restarted postoperatively (once acceptable hemostasis is achieved)
Moderate	• Hold warfarin for 4-5 days preoperatively. • Check the INR the day before surgery. Surgery can be performed if the INR is below 1.5. • Thromboprophylaxis(i.e., with LMWH or UFH) should be started preoperatively and should continue postoperatively (once acceptable hemostasis is achieved) until the INR is at a therapeutic level again with warfarin therapy.

High	• Effective therapeutic anticoagulation should be maintained :
	  • Hold warfarin for 4-5 days preoperatively and start therapeutic LMWH or UFH once the INR is below 2.0.
	  • If LMWH is used, hold 24 hours before the surgery.
	  • If IV UFH is used, hold the infusion 6 hours preoperatively.
	• Postoperatively, restart heparin therapy once acceptable hemostasis is achieved.:
	  • Restart warfarin.
	  • Stop heparin once the INR reaches a therapeutic level.

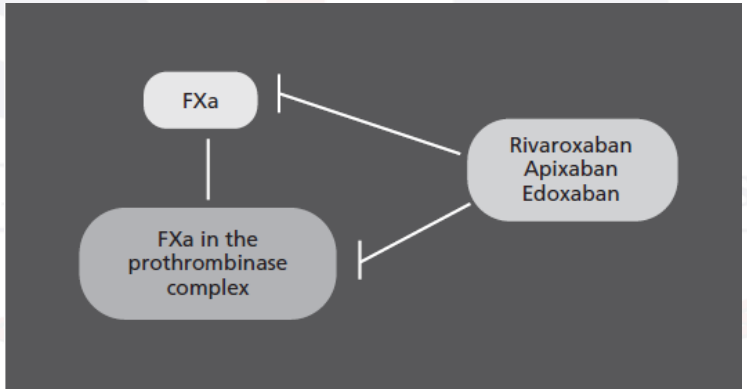
Adverse Effects

- *Skin necrosis:*
  - *Rare*
  - during initiation (or reinitiating if stopped) of treatment
  - Made worse by administration of **large loading doses**.
  - One third of cases occur in patients with underlying heterozygote/homozygote hereditary protein C deficiency
- Fetal complications:
  - Coumarin embryopathy: in the first trimester (specifically between weeks 6 and 12) has been associated with the development of with its characteristic nasal hypoplasia and stippled epiphyses. Limb hypoplasia
  - Central nervous system (CNS) malformations :
    - exposure to VKAs during any trimester
    - dorsal- and ventral-midline dysplasia.
  - Bleeding complications in the fetus or neonate.
    - warfarin use at any time during pregnancy easily crosses the placenta

Factor Xa Inhibitors

Products & Pharmachological categories

- **Indirect Anti Xa activity through binding to AT III**: Fondaparinux
  - Synthetic pentasaccharide: binds to ATIII , increases the affinity of AT for factor Xa (approximately 300-fold) without thrombin inhibition activity because it needs 18 polysaccharides chain
  - Parenteral : Once daily SC injection
  - Approved for children >1 Y
  - Few reports of cross-reactivity with HIT Ab
- **Direct Anti Xa activity through binding to FXa**: Rivaroxaban; Apixaban ;Edoxaban
  - Highly selective and direct inhibitor of activated factor X (Xa), both bound and unbound Xa
  - Oral
  - Not approved yet for children
  - Safe use in HIT



Oral Direct Anti Xa drugs

Table 12.1 Pharmacologic characteristics of oral direct factor Xa inhibitors in late clinical development

	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Selective direct factor Xa inhibitor	Selective direct factor Xa inhibitor	Selective direct factor Xa inhibitor
Oral bioavailability (%)	80–100 (100% WITH FOOD)	60	50
Half-life (hours)	7–13	8–15	6–11
Renal elimination (%)	66 (33 unchanged and 33 inactive metabolite)	22	36–45
Time to maximum inhibition (hours)	1–4	1–4	1–4
Potential drug interactions	Potent inhibitor of CYP3A4 and P-gp*	Potent inhibitor of CYP3A4**	Potent inhibitor of CYP3A4 and P-gp*

*Potent inhibitors of both CYP3A4 and P-gp include antifungals (e.g., ketoconazole, intraconazole, voriconazole, posaconazole) and protease inhibitors (e.g., ritonavir).
**Potent CYP3A4 inhibitors include azole antifungals, macrolide antibiotics (e.g., clarithromycin), and protease inhibitors (e.g., atanazavir).
P-gp, P-glycoprotein.

- CYP 3A4 inhibitors can lead to increased drug bioavailability and may predispose to bleeding
- Potent cytochrome inducers (e.g., rifampicin) can have the opposite effect and significantly reduce available drug

	Rivaroxaban	Apixaban
Laboratory monitoring	no specific laboratory parameters available to monitor : • .A transient dose-dependent prolongation of aPTT and PT may be seen 1-4 hours after administration not applicable at therapeutic levels • Antifactor Xa levels were originally designed and calibrated for LMWH and must be specifically calibrated for Factor Xa inhibitors	
Reversal	• no specific reversal agent exists • In patients with normal renal function, treatment of minor events may be handled simply by cessation of rivaroxaban • Four-factor PCC may be the best option currently available for major events/prompt blood stop need (Thrombosis and Hemostasis Society of North America ; German Society of Neurology)	
Daily dosage frequency	Once-twice	twice
Renal failure	• Dose reduction is necessary in patients with stable chronic kidney disease, • Contraindicated in patients with severe renal (CrCl < 30 mL/min) or hepatic insufficiency	minimize need for dose adjustment
Hepatic failure	Dose reduction and clinical F/U	Dose reduction and clinical F/U
On going clinical trials	RECORD; EINSTEIN-EXT; EINSTEIN-DVT;ROCKET; MEGALLEN	AMPLIFY-EXT;ADVANCE; ARISTOTLE

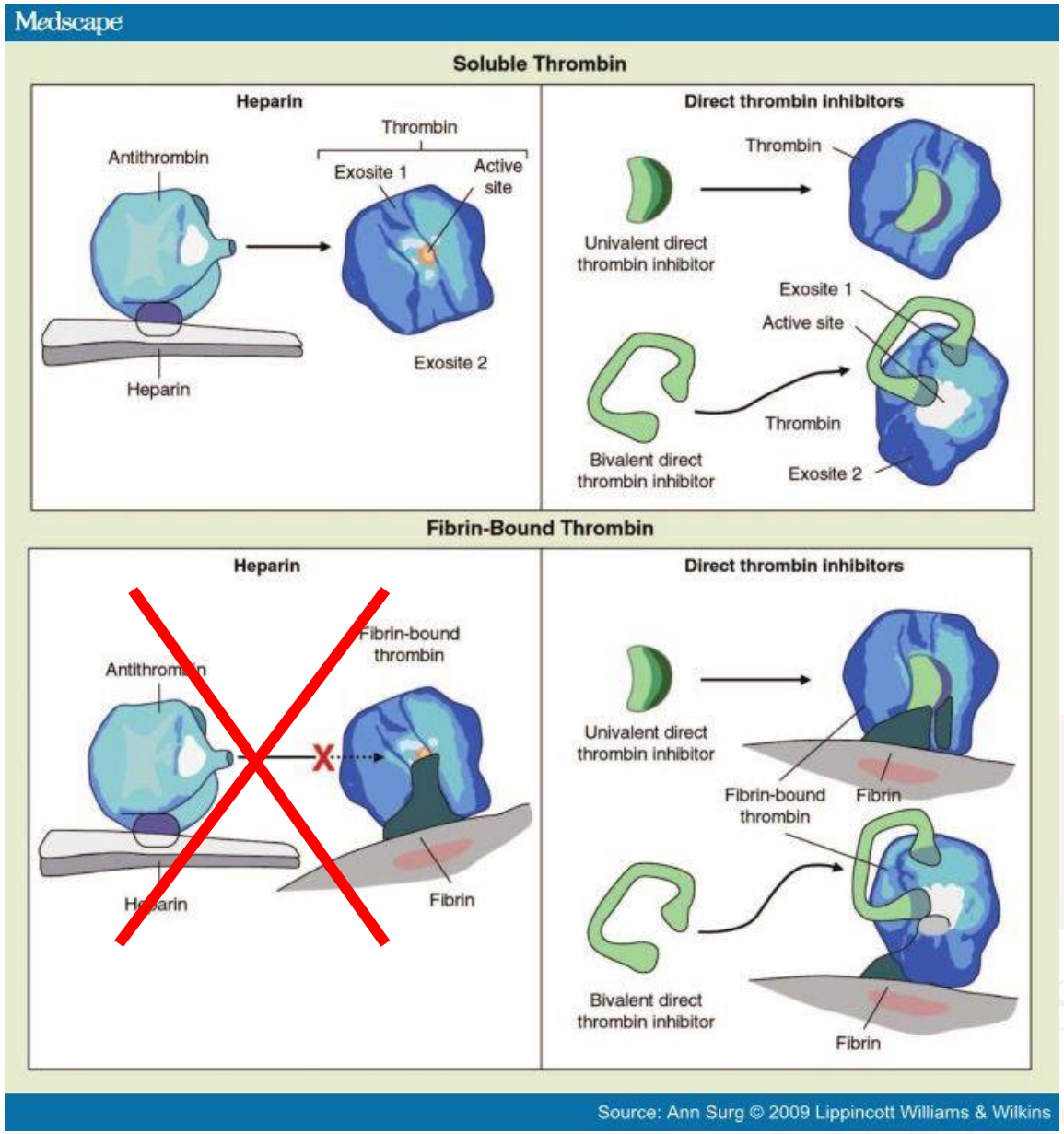
Fondaparinux

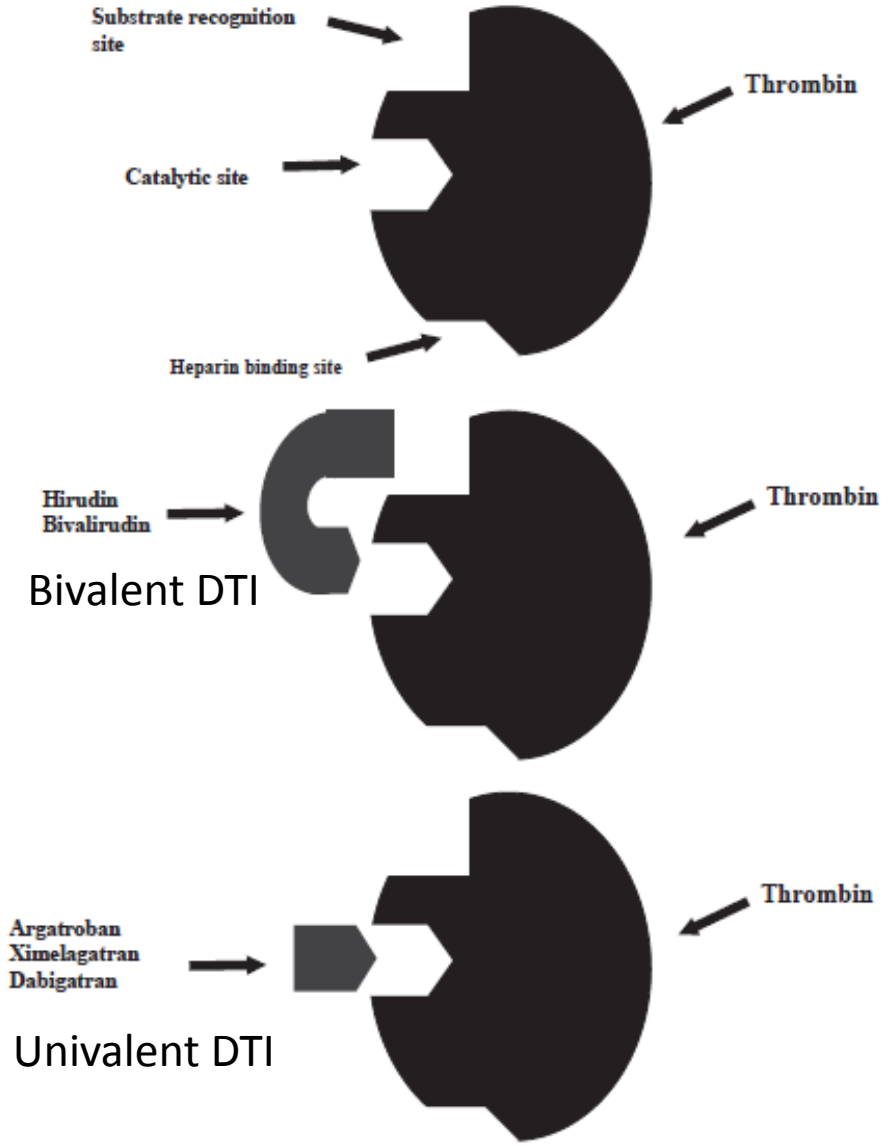
- Pharmacologically active only when bound to AT:
  - Decreased activity in **AT deficiency**
  - **Activity is saturable** and antithrombotic effect of the drug reaches a plateau once there is no free AT
- Unlike heparin, effectively inhibits thrombin generation in platelet-rich plasma, which suggests **absence of interaction between Fondaparinux and platelet proteins**, such as platelet factor 4
- inhibit FXa unbound and bound to clot, BUT **unable to inhibit factor Xa already included in the prothrombinase complex**

Fondaparinux: PK & applications

- After a SC dose of 2.5 mg :
  - Time to reach Cmax =1.7 ± 0.4 hours.
  - The bioavailability is complete
  - Plasma half-life is **17 hours** in young individuals and **21 hours** in the elderly
  - The steady-state is reached after **3–4 days**.
- 64–77% of Fondaparinux is excreted unmodified in urine for up to 72 hours: **dose adjustment is needed in renal failure**
- Fondaparinux does not influence the effect of warfarin on INR :
  - The INR may thus be used to monitor the effect of oral anticoagulants during coadministration of both drugs
  - Has approval in the setting of **bridging to warfarin therapy** for the treatment of PE and DVT
- Nearly completely bound to AT, it is not immediately available for placental transfer: may be an alternative to heparin in **pregnancy**.

Direct Thrombin Inhibitor (DTI)


Medscape
Soluble Thrombin
Heparin
Thrombin
Antithrombin
Exosite 1
Active site
Exosite 2
Heparin
Direct thrombin inhibitors
Thrombin
Univalent direct thrombin inhibitor
Exosite 1
Active site
Thrombin
Bivalent direct thrombin inhibitor
Exosite 2
Fibrin-Bound Thrombin
Heparin
Fibrin-bound thrombin
Fibrin
Direct thrombin inhibitors
Univalent direct thrombin inhibitor
Fibrin-bound thrombin
Fibrin
Bivalent direct thrombin inhibitor
Fibrin
Source: Ann Surg © 2009 Lippincott Williams & Wilkins


Substrate recognition site
Thrombin
Catalytic site
Heparin binding site
Hirudin
Bivalirudin
Thrombin
Bivalent DTI
Argatroban
Ximelagatran
Dabigatran
Thrombin
Univalent DTI

Overview of DTIs

- DTIs have several potential advantages over heparins including:
  - **Not** subject to steric hindrance and can **inactivate clot-bound thrombus**
  - **Do not** require a **cofactor** to exert their effect
  - **Do not** have any **inhibitors** such as platelet factor 4 and heparinase
  - **Do not** bind to **plasma proteins** and tissues which alter its bioavailability and pharmacokinetics.
  - **Do not** cause immune-mediated syndromes of **HIT**
  - There is **no** platelet activation with DTIs
- DTI products:
  - Parentral: Argatroban ;Bivalirubin
  - Oral: Dabigatran

Table 10.1 Properties and Food and Drug Administration (FDA) indications for the use of parenteral direct thrombin inhibitors

Characteristic	Hirudin	Bivalirudin	Argatroban
Type of molecule	65 amino acids	20 amino acid peptide	Synthetic arginine derivative
Molecular weight (Da)	7000	1980	527
Thrombin-binding site	Catalytic and exocite 1	Catalytic and exocite 1	Catalytic
Thrombin-binding kinetics	Irreversible	Reversible on proteolytic cleavage	Reversible and competitive
Clearance	Renal	Endogenous peptidases and minor renal	Hepatic
Elimination half-life (minutes)	60	25	54
Antibodies	Yes	No	No
FDA indications	Treatment of HIT	Anticoagulation in PCI, NSTEMI, and STEMI	Treatment in HIT PCI in patients with HIT or at risk for HIT

HIT, heparin-induced thrombocytopenia; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Antibodies to hirudin occur in up to 40% of patients and anaphylactic reactions can occur

	ARGATROBAN	BIVALIRUDIN
Dose adjustment	**Hepatic failure**	**Renal failure**
Monitoring	**aPTT>1.5-3 times NL base line**	
Adverse effects	• **Bleeding** • **Warfarin initiation and bridging can be problematic**	• **Bleeding** • **the most frequent : hypotension, nausea, and back pain,**
Reverse of the effects	• **Discontinue immediately + local measures lead to NL aPTT after 2 Hr**	• **Normal renal function:Discontinue immediately + local measures** • **CRF/Immediate reversal: using hemodialysis or plasmapheresis.**
Main clinical preference(s)	**prevention and treatment of thromboembolism in the context of HIT**	**its significant non–organ dependent metabolism, which makes it an attractive option in critically ill patients**
Used in HIT	**+++**	**+**
Used in children	**+**	**+**

TABLE 26-7 Comparison of Properties of Parenteral Anticoagulant Agents

	UFH	LMWH	Fondaparinux	Lepirudin	Bivalirudin	Argatroban
Size	Very large	Large	Small	Small	Small	Very small
Molecular weight (Da)	15,000	5000	1728	7000	2180	527
Thrombin inhibition	Indirect	Indirect	None	Direct	Direct	Direct
Thrombin-binding affinity	++	+	None	+++	++	++
Route	IV, SC	SC, IV	SC	IV, SC	IV	IV
Onset	Rapid	Rapid	Rapid	Rapid	Rapid	Rapid
Offset	Rapid	Slower	Slow	Slow	Rapid	Rapid
Reversible	Yes	Partial	No	No	No	No
Clearance	Hepatic	Renal	Renal	Renal	Proteolysis, renal	Hepatic
Inhibition of clot-bound factor	No	No	No	Yes	Yes	Yes
Tests for monitoring	PTT, anti–factor Xa	Anti–factor Xa	Anti–factor Xa	PTT, ACT	PTT, ACT	PTT, ACT

DABIGATRAN : PK

- Prodrug
- Bioavailability : <10% after oral absorption
- Substrate of the **P-glycoprotein drug transporter** : drug interaction with medications that inhibit or induce P-glycoprotein (e.g., ketoconazole, quinidine, amiodarone, verapamil) or limit its bioavailability (e.g., proton pump inhibitors [PPIs])
- Metabolized in **liver** and converted to active drug
- Dose **not** interact with CYP-450
- Short half-life of 12 to 14 hours,
- Maximum effect is achieved within **2 to 3 hours** of ingestion
- Drug elimination is mostly through the kidneys (approximately 80%):
  - Contraindicated in CRF; dose adjustment required

DABIGATRAN : administration and monitoring

- Wide therapeutic window : fixed doses (110 and 150 mg bid) in patients with a glomerular filtration rate above 30 mL/min

- Reverse effect:
  - normal renal function and minor bleeds, drug discontinuation
  - Renal failure /immediate reverse: dialysis and activated charcoal administration
- Laboratory evaluation :
  - Thrombin time (TT) ; Ecarin clotting time (ECT);Diluted TT: not widely available
  - **activated partial thromboplastin time (aPTT)** increased in a a non-linear dose response curve : normal aPTT excludes the presence of significant amounts of a DTI, but the degree of elevation of the aPTT does not necessarily correlate with DTI activity

Q&A