Introduction and review of Anticoagulant drugs

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Refferences :

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Overview & Categories

• Anticoagulants:
  • Heparin
    • Unfractionated Heparin
    • Low Molecular Weight Heparin: Dalteparin; Enoxaparin; Tinzaparin
  • Vitamin K Antagonists: Warfarin; Acenocoumoral; Phenprocoumon
  • Factor Xa Inhibitors: Fondaparinux; Rivaroxaban; 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: Dipyridamol
  • Protease Activated Receptor-1 (PAR) antagonists: Atofapaxar; Vorapaxar
  • GP IIb-IIIa inhibitors: Abciximab, Tirofibian, and Eptifibatide

• 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)
• $T_{1/2}$:
  • 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
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

<table>
<thead>
<tr>
<th>PTT (sec)</th>
<th>Bolus Doses (U)</th>
<th>Stop Infusion (min)</th>
<th>Change in Infusion‡</th>
<th>Time of Repeat PTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>5000</td>
<td>0</td>
<td>+3 mL/hr</td>
<td>6 hr</td>
</tr>
<tr>
<td>50-59</td>
<td>0</td>
<td>0</td>
<td>+3 mL/hr</td>
<td>6 hr</td>
</tr>
<tr>
<td>60-85</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Next morning</td>
</tr>
<tr>
<td>86-95</td>
<td>0</td>
<td>0</td>
<td>-2 mL/hr</td>
<td>Next morning</td>
</tr>
<tr>
<td>96-120</td>
<td>0</td>
<td>30</td>
<td>-2 mL/hr</td>
<td>6 hr</td>
</tr>
<tr>
<td>&gt;120</td>
<td>0</td>
<td>60</td>
<td>-4 mL/hr</td>
<td>6 hr</td>
</tr>
</tbody>
</table>

### WEIGHT-BASED NOMOGRAM

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.

<table>
<thead>
<tr>
<th>PTT (sec)§</th>
<th>Bolus (U/kg)</th>
<th>Infusion (U/kg/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>80</td>
<td>Increase rate by 4</td>
</tr>
<tr>
<td>35-45</td>
<td>40</td>
<td>Increase rate by 2</td>
</tr>
<tr>
<td>46-70</td>
<td>0</td>
<td>No change</td>
</tr>
<tr>
<td>71-90</td>
<td>0</td>
<td>Decrease rate by 2</td>
</tr>
<tr>
<td>&gt;90</td>
<td>0</td>
<td>Decrease rate by 3</td>
</tr>
</tbody>
</table>

*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.
PPT, 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 anti–factor Xa levels.
Indications:

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


• 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 allergy, 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
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
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 prophylactic doses, even in patients with end-stage renal disease.
Monitoring

- The target anti–factor Xa level (few data to support the clinical utility):
  - twice-daily enoxaparin and nadroprarin = 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 nadroprarin, 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: 0.5 per 100 U of anti–factor Xa activity
VITAMIN K ANTAGONISTS
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


• 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

• Thrombophylaxis in patients with AF
• Treatment of DVT & PE
• Secondary prevention of VTE after an initial episode of DVT or PE
• Thromboprophylaxis 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>
<thead>
<tr>
<th>OBI</th>
<th>HEMORR$_2$HAGES</th>
<th>HAS-BLED</th>
<th>ATRIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 65 yr</td>
<td>Abnormal renal/liver function</td>
<td>Hypertension</td>
<td>Anemia</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>Alcohol abuse</td>
<td>Abnormal renal/liver function</td>
<td>Severe renal disease</td>
</tr>
<tr>
<td>Prior gastrointestinal bleeding</td>
<td>Cancer</td>
<td>Stroke</td>
<td>Age ≥ 75 yr</td>
</tr>
<tr>
<td>Recent myocardial infarction, diabetes,</td>
<td>Reduced platelet count or function</td>
<td>Bleeding</td>
<td>Any prior bleed</td>
</tr>
<tr>
<td>hemoglobin &lt; 30%, or creatinine &gt; 1.5 mg/dL</td>
<td>Rebleeding risk</td>
<td>Labile INR</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Low risk</td>
<td>Low risk</td>
<td>Elderly (&gt;65 yr)</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>≥3</td>
<td>Drugs or alcohol</td>
<td>≥4</td>
</tr>
</tbody>
</table>

INR, International normalized ratio; OBI, outpatient bleeding risk index.
### Treatment Plan:
On warfarin from 04-Feb-2014 to present for LV mural thrombus (post MI, LV aneurysm).

<table>
<thead>
<tr>
<th>Date</th>
<th>INR</th>
<th>Dose (mg/day)</th>
<th>Suggested Dose (mg/day)</th>
<th>Omiss (Days)</th>
<th>Review (Days)</th>
<th>Suggested Review (Days)</th>
<th>Next Test Date</th>
<th>DNA</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-Feb-2014</td>
<td>2.3</td>
<td>2.5</td>
<td>0</td>
<td>14</td>
<td></td>
<td></td>
<td>11-Mar-2014</td>
<td>-</td>
<td>Add Comment</td>
</tr>
<tr>
<td>04-Mar-2014</td>
<td>1.6</td>
<td>4.0</td>
<td>0</td>
<td>8</td>
<td></td>
<td></td>
<td>12-Mar-2014 09:15</td>
<td>-</td>
<td>Add Comment</td>
</tr>
</tbody>
</table>

### Daily INR Record

<table>
<thead>
<tr>
<th>Date</th>
<th>Day</th>
<th>Dose (mg)</th>
<th>Taken</th>
<th>Notes</th>
</tr>
</thead>
</table>

### Food Diary / Menu Planner

#### Breakfast
- Monday
- Tuesday
- Wednesday
- Thursday
- Friday
- Saturday
- Sunday

#### Lunch
- Monday
- Tuesday
- Wednesday
- Thursday
- Friday
- Saturday
- Sunday

#### Dinner
- Monday
- Tuesday
- Wednesday
- Thursday
- Friday
- Saturday
- Sunday

### 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.

### Summary
- Total Vitamin K
- Total Protein

---

**Daily INR Record**

**Start Date: MON TUE WED THU FRI SAT SUN**

**Warfarin Dosage (mg)**

**Date**

**Day**

**Dose**

**Taken**

**Notes**
Adverse Effects

• **Bleeding:**
  • 3% to 5% per year.
  • **Personalized risk estimates:**
    • Outpatient Bleeding Risk Index
    • HEMORR2HAGES score  
    
  • 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


<table>
<thead>
<tr>
<th>Clinical Scenarios</th>
<th>Management Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Difficult-to-control INR</strong></td>
<td></td>
</tr>
<tr>
<td><strong>THE NONBLEEDING PATIENT</strong></td>
<td></td>
</tr>
</tbody>
</table>
| INR 3.0-4.5                | 1. Warfarin withdrawal ± 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 ± 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

<table>
<thead>
<tr>
<th>Risk of thrombotic recurrence:</th>
<th>Management</th>
</tr>
</thead>
</table>
| **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 & Pharmacological 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

- 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

| Table 12.1 Pharmacologic characteristics of oral direct factor Xa inhibitors in late clinical development |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|
| Rivaroxaban                                       | Apixaban                                         | Edoxaban                                         |
| Mechanism of action                              | Mechanism of action                              | 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.
<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laboratory monitoring</strong></td>
<td>no specific laboratory parameters available to monitor:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• A transient dose-dependent prolongation of aPTT and PT may be seen 1-4 hours after administration not applicable at therapeutic levels</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Antifactor Xa levels were originally designed and calibrated for LMWH and must be specifically calibrated for Factor Xa inhibitors</td>
<td></td>
</tr>
<tr>
<td><strong>Reversal</strong></td>
<td>• no specific reversal agent exists</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• In patients with normal renal function, treatment of minor events may be handled simply by cessation of rivaroxaban</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 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)</td>
<td></td>
</tr>
<tr>
<td><strong>Daily dosage frequency</strong></td>
<td>Once-twice</td>
<td>twice</td>
</tr>
<tr>
<td><strong>Renal failure</strong></td>
<td>• Dose reduction is necessary in patients with stable chronic kidney disease,</td>
<td>minimize need for dose adjustment</td>
</tr>
<tr>
<td></td>
<td>• Contraindicated in patients with severe renal (CrCl &lt; 30 mL/min) or hepatic insufficiency</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatic failure</strong></td>
<td>Dose reduction and clinical F/U</td>
<td>Dose reduction and clinical F/U</td>
</tr>
<tr>
<td><strong>On going clinical trials</strong></td>
<td>RECORD; EINSTEIN-EXT; EINSTEIN-DVT;ROCKET; MEGALLEN</td>
<td>AMPLIFY-EXT;ADVANCE; ARISTOTLE</td>
</tr>
</tbody>
</table>
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)
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:
  • Parenteral: Argatroban; Bivalirubin
  • Oral: Dabigatran
Antibodies to hirudin occur in up to 40% of patients and anaphylactic reactions can occur.

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

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

HIT, heparin-induced thrombocytopenia; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.
<table>
<thead>
<tr>
<th></th>
<th>ARGATROBAN</th>
<th>BIVALIRUDIN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose adjustment</strong></td>
<td>Hepatic failure</td>
<td>Renal failure</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td></td>
<td>aPTT &gt; 1.5-3 times NL base line</td>
</tr>
<tr>
<td><strong>Adverse effects</strong></td>
<td>• Bleeding</td>
<td>• Bleeding</td>
</tr>
<tr>
<td></td>
<td>• Warfarin initiation and bridging can be problematic</td>
<td>• the most frequent: hypotension, nausea, and back pain,</td>
</tr>
<tr>
<td><strong>Reverse of the effects</strong></td>
<td>• Discontinue immediately + local measures lead to NL aPTT after 2 Hr</td>
<td>• Normal renal function: Discontinue immediately + local measures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CRF/Immediate reversal: using hemodialysis or plasmapheresis.</td>
</tr>
<tr>
<td><strong>Main clinical preference(s)</strong></td>
<td>prevention and treatment of thromboembolism in the context of HIT</td>
<td>its significant non–organ dependent metabolism, which makes it an attractive option in critically ill patients</td>
</tr>
<tr>
<td><strong>Used in HIT</strong></td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Used in children</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Property</td>
<td>UFH</td>
<td>LMWH</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-----------</td>
<td>----------</td>
</tr>
<tr>
<td>Size</td>
<td>Very large</td>
<td>Large</td>
</tr>
<tr>
<td>Molecular weight (Da)</td>
<td>15,000</td>
<td>5000</td>
</tr>
<tr>
<td>Thrombin inhibition</td>
<td>Indirect</td>
<td>Indirect</td>
</tr>
<tr>
<td>Thrombin-binding affinity</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Route</td>
<td>IV, SC</td>
<td>SC, IV</td>
</tr>
<tr>
<td>Onset</td>
<td>Rapid</td>
<td>Rapid</td>
</tr>
<tr>
<td>Offset</td>
<td>Rapid</td>
<td>Slower</td>
</tr>
<tr>
<td>Reversible</td>
<td>Yes</td>
<td>Partial</td>
</tr>
<tr>
<td>Clearance</td>
<td>Hepatic</td>
<td>Renal</td>
</tr>
<tr>
<td>Inhibition of clot-bound factor</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Tests for monitoring</td>
<td>PTT, anti-factor Xa</td>
<td>Anti-factor Xa</td>
</tr>
</tbody>
</table>
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 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