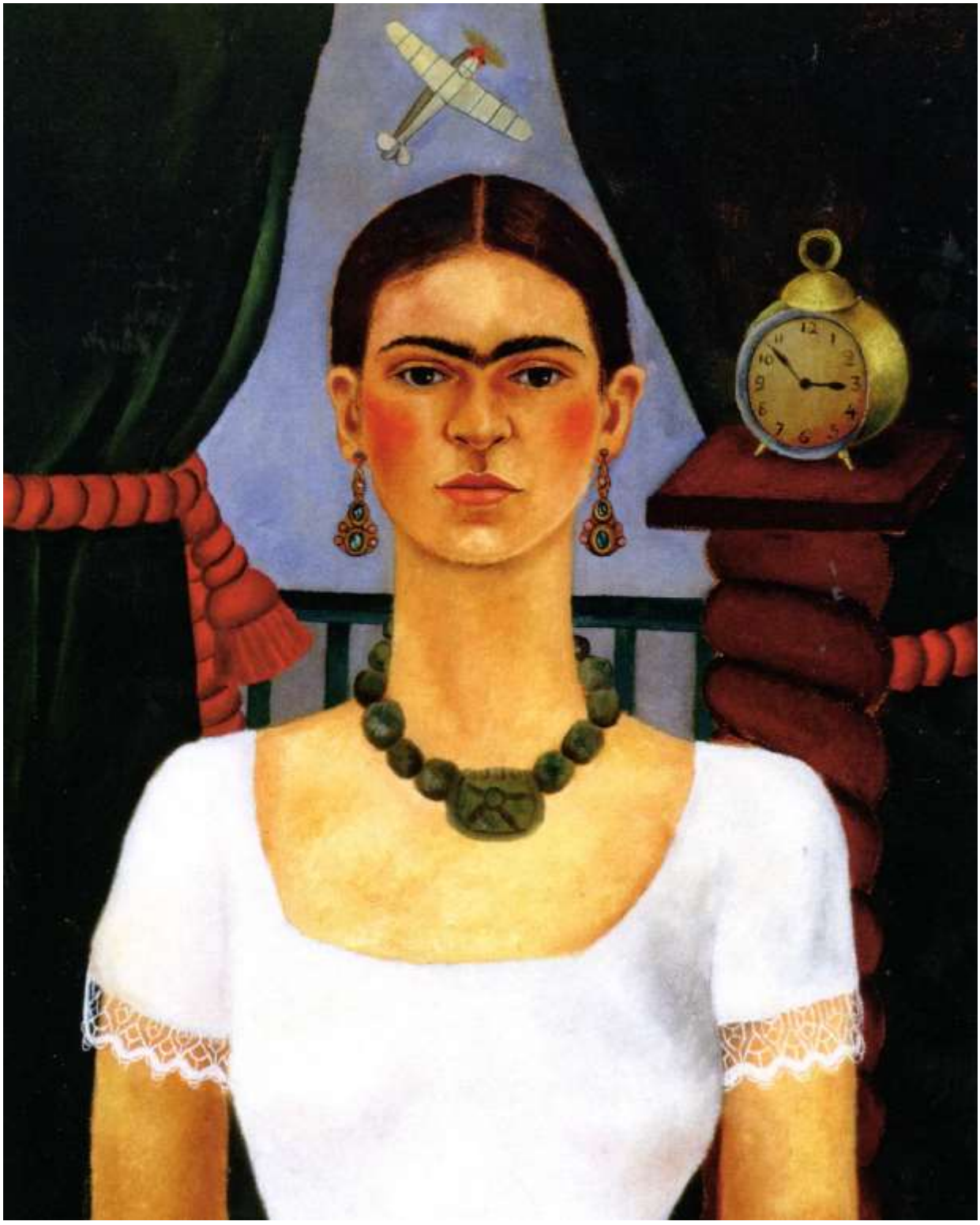
THE NORTHERN HOSPITAL

DABIGATRAN



"Self Portrait - Time Flies", oil on board, 1929, Frida Kahlo.

Just before I went to Cuernavaca, there occurred one of the happiest events of my life. I was at work on one of the uppermost frescos of the Ministry of Education building one day, when I heard a girl shouting up to me, "Diego, please come down from there! I have something important to discuss with you!"

I turned my head and looked down from my scaffold. On the ground beneath me stood a girl of about eighteen. She had a fine nervous body, topped by a delicate face. Her hair was long; dark and thick eyebrows met above her nose. They seemed like the wings of a blackbird, their black arches framing two extraordinary brown eyes.

When I climbed down she said, "I didn't come here for fun. I have to work to earn my livelihood. I have done some paintings which I want you to look over professionally. I want an absolutely straight forward opinion because I cannot afford to go on just to appease my vanity. I want you to tell me whether you think I can become a good enough artist to make it worth my while to go on. I've brought three of my paintings here. Will you come and look at them?"

"Yes", I said, and followed her to a cubicle under a stairway where she had left her paintings.

She turned each of them, leaning against the wall to face me. They were all three portraits of women. As I looked at them, one by one, I was immediately impressed. The canvases revealed an unusual energy of expression, precise delineation of character, and true severity. They showed none of the tricks in the name of originality that usually mark the work of ambitious beginners. They had a fundamental plastic honesty, and an artistic personality of their own. They communicated a vital sensuality, complimented by a merciless yet sensitive power of observation. It was immediately obvious to me that this girl was an authentic artist.

She undoubtedly noticed the enthusiasm in my face, for before I could say anything, she admonished me in a harshly defensive tone. "I have not come to you looking for compliments. I want the criticism of a serious man". I'm neither an art lover nor an amateur. I'm simply a girl who must work for a living".

I felt deeply moved by admiration for this girl. I had to restrain myself from praising her as much as I wanted to. Yet I could not be completely insincere. I was puzzled by her attitude. Why, I asked her, didn't she trust my judgement? Hadn't she come herself to ask for it?

"The trouble is" she replied, "that some of your good friends have advised me not to put too much stock in what you say. They say that if it's a girl who asks your opinion and she's not an absolute horror, you are ready to gush all over her. Well, I want you to tell me only one thing. Do you actually believe that I should continue to paint, or should I turn to some other sort of work?".

"In my opinion, no matter how difficult it is for you, you must continue to paint," I answered at once.

"Then I'll follow your advice. Now, I'd like to ask you one more favour. I've done other paintings which I'd like you to see. Since you don't work on Sundays, could you come to my place next Sunday to see them? I live in Coyoacan, Avenida Londres 125. My name is Frida Kahlo".

The moment I heard her name, I remembered that my friend, Lombardo Toledano, while Director of the National Preparatory School, had complained to me about the intractability of a girl of that name. She was the leader, he said, of a band of juvenile delinquents who raised such uproars in the school that Toledano had considered quitting his job on account of them. I recalled him once pointing her out to me after depositing her in the principal's office for a reprimand. Then another image popped into my mind, that of the twelve year old girl who had defied Lupe, seven years before, in the auditorium of the school where I had been painting murals.

I said, "But you are...."

She stopped me quickly, almost putting her hand on my mouth in her anxiety. Her eyes acquired a devilish brilliancy.

Threateningly, she said, "Yes, so what? I was that girl in the auditorium, but that has absolutely nothing to do with now. You still want to come Sunday?"

I had great difficulty not answering, "More than ever! But if I showed my excitement she might not let me come at all. So I only answered, "Yes".

Then after refusing my help in carrying her paintings, Frida departed, the big canvases jiggling under her arms.

Next Sunday found me in Coyoacan looking for Avenida Londres, 126. When I knocked on the door, I heard someone over my head, whistling "The Internationale". In the top of a high tree, I saw Frida in overalls, starting to climb down Laughing gaily, she took my hand and ushered me through the house, which seemed to be empty, and into her room. Then she paraded all her paintings before me. These, her room, her sparkling presence, filled me with a wonderful joy.

I did not know it then, but Frida had already become the most important fact in my life. And she would continue to be up to the moment she died, twenty seven years later.

A few days after the visit to Frida's home I kissed her for the first time. When I had completed my work in the Education building, I began courting her in earnest. Although she but twenty one and I more than twice her age, neither of us felt the least bit awkward. Her family, too, seemed to accept what was happening.

One day her father, Don Guillermo Kahlo, who was an excellent photographer, took me aside.

"I see you're interested in my daughter, eh?", he said.

"Yes", I replied. "Otherwise I would not be coming all the way out to Coyoacan to see her".

"She is a devil", he said.

"I know it"

"Well, I've warned you!", he said, and he left.

Diego Rivera, My Art, My Life

Diego would become Frida's teacher and mentor. We first see evidence of his influence on her work "Time Flies" 1929. It is an evolutionary stage away from the traditional European style of the time towards a novel and uniquely Mexican oeuvre. The first almost child-like steps of symbolism which would strongly hallmark all of her future works is seen in the simplistic images of the clock and an aircraft, that allude to the title of the work.

Frida Kahlo, photographed by Guillermo Davila, 1929.

Two of the most volatile personalities of the Artistic world of the Twentieth century - happen to have been husband and wife - the brilliant and revolutionary Mexican Artists, Diego Rivera and Frida Kahlo. It would be a most tempestuous relationship. Both however went into their marriage with their eyes wide open, despite even, the advice of Frida's own father to his prospective son in law - "She is a devil", he warned him! When we prescribe an anticoagulant agent to our patients they must go into this partnership with their eyes wide open. We must, like Guillermo, give due warning of the potential difficulties, making sure that the patient well understands the potential for serious, or even life-threatening bleeding.

DABIGATRAN

Introduction

Dabigatran is a drug from a novel class of non-coumarin anticoagulants, loosely known as **NOACs** or "**N**ew **O**ral **A**nti**c**oagulants" or alternately as **DOACs** or "**D**irect acting **O**ral **A**nti-**C**oagulants".

It is an orally active **direct competitive thrombin inhibitor.**

It offers some significant therapeutic advantages over warfarin.

The major adverse effect of dabigatran is, as with all anticoagulant agents, **bleeding.**

The specific antidote / reversal agent for dabigatran is idarucizumab.

See also separate document on idarucizumab (in Drugs folder).

History

Dabigatran (originally only known as compound BIBR 953) was discovered from a panel of chemicals with similar structures to the benzamidine based thrombin inhibitor α-NAPAP

It was first approved for clinical use in Europe in 2008.

Classification

The anticoagulants can be classified thus:

1. **The NOACs:**
    - **Direct Acting Competitive Thrombin Inhibitors:**
        - ♥ **Dabigatran**
        - ♥ Bivalirudin
    - **Direct Acting Factor Xa Inhibitors:**
        - ♥ Rivaroxaban
        - ♥ Apixaban
        - ♥ Edoxaban
2. **Indirect Factor Xa & Thrombin Inhibitors:**

These greatly stimulate the activity of the naturally occurring **anti-thrombin III enzyme** which in turn **inhibits** the activity of Factor Xa and thrombin (and other proteases)

Agents include:

- Unfractionated Heparin (UFH)
- Fractionated or LMW heparins:
  - ♥ Enoxaparin (trade name Clexane)
  - ♥ Dalteparin (trade name Fragmin)
  - ♥ Nadroparin
  - ♥ Tinzaparin
  - ♥ Certoparin
  - ♥ Reviparin
  - ♥ Bemiparin
- Heparinoids:
  - ♥ Danaparoid

3. **Indirect factor Xa Inhibitors:**

- Fondaparinux

  Fondaparinux is a **synthetic** indirect inhibitor of Factor Xa. Its structure is based on the natural pentasaccharide contained within heparin and low-molecular-weight heparins (LMWHs)

4. **Vitamin K Antagonists:**

4-Hydroxycoumarins:

- Warfarins
- Super-warfarins (used as rodenticides)

Preparations

Dabigatran etexilate as:

Capsules:

- 75 mg
- 110 mg
- 150 mg

Mechanism of Action

Dabigatran is a **direct competitive thrombin inhibitor.**

Since thrombin (serine protease) enables the conversion of **fibrinogen into fibrin** (**see appendix 1 below**) during the coagulation cascade, its inhibition prevents the development of thrombus.

Dabigatran inhibits *free* thrombin as well as *fibrin-bound* thrombin.

This action is in contrast to **warfarin**, which inhibits normal vitamin K metabolism, which is a co-factor that is required for the synthesis of the vitamin K dependent coagulation factors, II, VII, IX and X, (as well as proteins C and S).

It is in contrast to the heparins which are direct Antithrombin III *activators*, (which inhibit thrombin).

Pharmacodynamics

Dabigatran is a **direct thrombin inhibitor.**

The onset of action of dabigatran after oral dosing is rapid at around **30 minutes.**

Its duration of action is approximately **24 - 36 hours**, (but is also dependent on plasma concentration).

Advantages compared to warfarin:

- Fast onset of action:

  Onset of action is rapid, (within 2 hours) thereby potentially negating the need for initial treatment with a rapidly acting injectable anticoagulant.

- Fast offset of action:

  Anticoagulant effect lasts around 12 hours, which is much shorter than warfarin, (48-72 hours). This means toxic effects, if they occur, will not be as long lasting.

- Predictable response:

Anticoagulation response is sufficiently predictable that routine coagulation monitoring is not required - therefore avoids the need for repeated blood tests to monitor activity, and adjust dosages that warfarin therapy requires.

- Drug and food interaction:

  Dabigatran has a lower potential for food and drug interactions.

Disadvantages compared to warfarin:

- The routine coagulation monitoring tests (APTT / PT / INR) are *not* indicative of the anticoagulant effect of dabigatran.

- Dabigatran is a **direct competitive thrombin inhibitor** and not a clotting factor depleting agent, as is the case with warfarin. As such the administration of blood clotting products will not be wholly effective in reversing its effects.

  A specific antidote, **idarucizumab,** however is available

Pharmacokinetics

Absorption:

- Dabigatran is a hydrophilic polarised membrane-impermeable molecule which is not well absorbed after oral dosing.

  Dabigatran **etexilate** is a non-active small molecule *prodrug.*

  After oral administration dabigatran **etexilate** is rapidly absorbed then rapidly and completely converted to dabigatran by esterase-catalysed hydrolysis in plasma and in the liver.

- Peak plasma concentrations are on average attained within 2 hours

- The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate is only about 6.5%.

Distribution:

- The Vd of dabigatran is approximately 60 - 70 L thus exceeding the volume of total body water and so indicating a moderate *tissue* distribution.

- It is *not* highly protein bound, (around 35%).

- Dabigatran can cross the human placenta

- It is unknown if dabigatran is excreted into human breast milk.

Metabolism and excretion:

- **Dabigatran is predominantly excreted by the kidneys, unchanged.**

  The NOACs in general are renally excreted which requires that patients have their renal function checked **prior to initiation** of therapy and **repeated periodically** to avoid inadvertent overdose due to impaired clearance in renal dysfunction.

- The half-life (and duration of action) is approximately **12 -17 hours**.

- This half-life will be *prolonged* in patients with significant renal impairment/ failure.

Indications

Current approved indications for dabigatran include:

1. Prevention of VTE after elective total hip or knee replacement

2. Treatment of acute VTE and prevention of subsequent VTE

3. Non-valvular AF and a high risk of stroke or systemic embolism

Contraindications/ Precautions

1. Known hypersensitivity to dabigatran.

2. Patients with clinically significant active bleeding (contraindicated).

3. Patients with lesions at increased risk of clinically significant bleeding (contraindicated).

4. Patients with coagulopathies (contraindicated):

   - Including patients with significant hepatic disease (including moderate to severe hepatic impairment),which is associated with coagulopathy.

5. Patients with severe uncontrolled hypertension

6. Patients prone to **recurrent falls.**

7. Renal impairment:

   - Contraindicated if Cr Cl < 30 mL/minute; reduce dosage if Cr Cl 30-50 mL/minute (reduced clearance in renal impairment).

8. Hepatic impairment:

- Manufacturer contraindicates use if liver enzymes are > 2 times ULN or if hepatic disease may affect survival (no data). [2]

9. Elderly:

   - Reduce dose in people > 75 years taking dabigatran for AF or treatment of VTE and prevention of subsequent VTE (risk of bleeding is increased).

     Monitor renal function at least annually.

10. Spinal injection or puncture

    - Seek specialist advice before considering intrathecal or epidural analgesia or anaesthesia, or lumbar puncture (risk of epidural haematoma, which may cause paralysis).

Pregnancy:

Dabigatran is a category C drug with respect to pregnancy.

It is contraindicated by manufacturers.

Category C drugs are those drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Specialised texts should be consulted for further details.

Published reports describing the use of dabigatran during pregnancy have not been located.

Due to potential adverse fetal effects, consider an alternative medicine with more safety information in women who are planning to become pregnant and during pregnancy.

Breast feeding:

Published reports describing the use of dabigatran during breastfeeding have not been located.

Due to potential adverse effects in the breastfed infant, consider an alternative therapy during breastfeeding if possible.

Adverse Effects

1. Bleeding:

   - The principle adverse effect of dabigatran is, as for all NOACs and anticoagulants in general, is bleeding.

2. Hypersensitivity reactions, (rare)

Dosing [2]

Consider the use of a **warning bracelet** for patients.

Prevention of VTE after knee/hip replacement:

Treat for 10 days after knee replacement and 28 - 35 days after hip replacement.

Adult, initially 110 mg within 1 - 4 hours of completed surgery, then 220 mg once daily. If dabigatran cannot be started on the day of surgery, give 220 mg once daily.

Cr Cl 30-50 mL/minute, Adult, 150 mg once daily.

AF and acute VTE and prevention of subsequent VTE:

For VTE, treat with a parenteral anticoagulant for at least 5 days before starting dabigatran.

Continue dabigatran for at least 3 months.

Adult, 150 mg twice daily.

Increased risk of major bleeding or > 75 years, *Adult*, 110 mg twice daily.

Note that the reason for 5 days of initial enoxaparin is because that was the way the initial trials were designed and FDA approval was given on that basis. Also it is important to note that Dabigatran is not indicated on PBS in Australia for the treatment of DVT and PE (unless the patient has concurrent AF).

Rivaroxaban / apixaban is currently the preferred treatment.

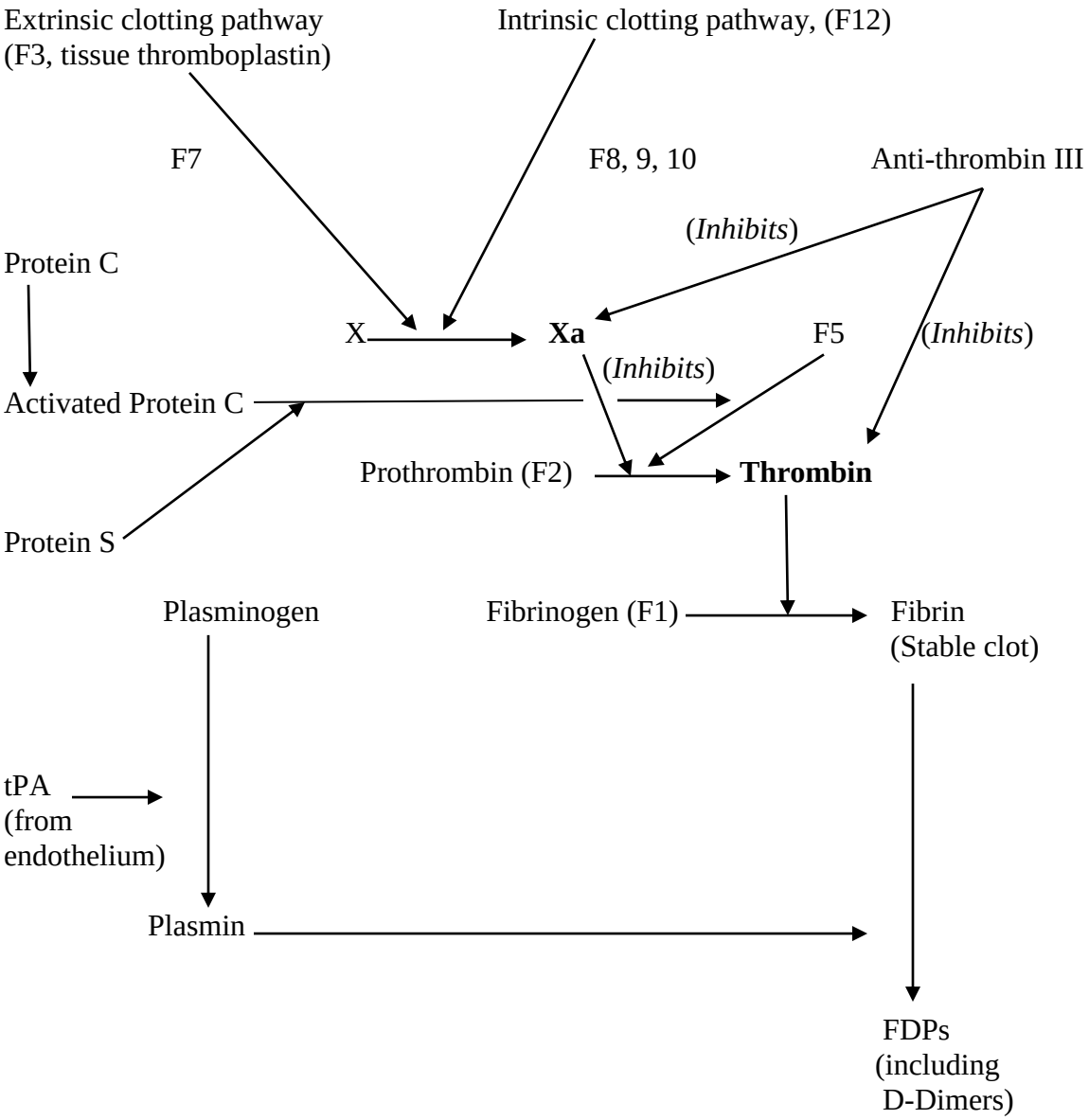
Reversal Agent:

The specific antidote / reversal agent for dabigatran is idarucizumab.

See also separate document on idarucizumab (in Drugs folder).

Appendix 1

The coagulation cascade and fibrinolytic system:



Appendix II

Note on the estimation of renal function for dabigatran dosing:

For the purpose of dabigatran (Pradaxa) dosing, renal function should be estimated by the Cockcroft-Gault method.

It is not appropriate to use the eGFR (MDRD method, corrected to a BSA of 1.73kg/m^2 - that is automatically reported in most pathology reports) particularly in elderly and or underweight patients where eGFR typically overestimates renal function.

Cockcroft-Gault CrCl = (140-age) x weight (kg)] x 1.23 / Creat (umol/L)

(*Correct by multiplying by 0.85 if female patient*).

References

1. **Australasian Society of Thrombosis and Haemostasis (ASTH)** H. Tran et al. New oral anticoagulants: A Practical Guide on Prescription, Laboratory Testing and Peri-procedural/bleeding Management. *Internal Medicine Journal* 44 (2014).

   - doi:10.1111/imj.12448.

2. Dabigatran in Australian Medicines Handbook Website, Accessed June 2019

3. Dabigatran in MIMs Website 1 November 2018.

4. Idarucizumab Boehringer Ingelheim: Reference ID: 3834358 2015.

5. Charles V. Pollack et al. Idarucizumab for Dabigatran Reversal. NEJM 2015; 373:511-20. DOI: 10.1056/NEJMoa1502000

6. Dabigatran in RWH Pregnancy & Breastfeeding Guidelines, 16 October 2017

Dr J. Hayes
Reviewed 2 July 2019.