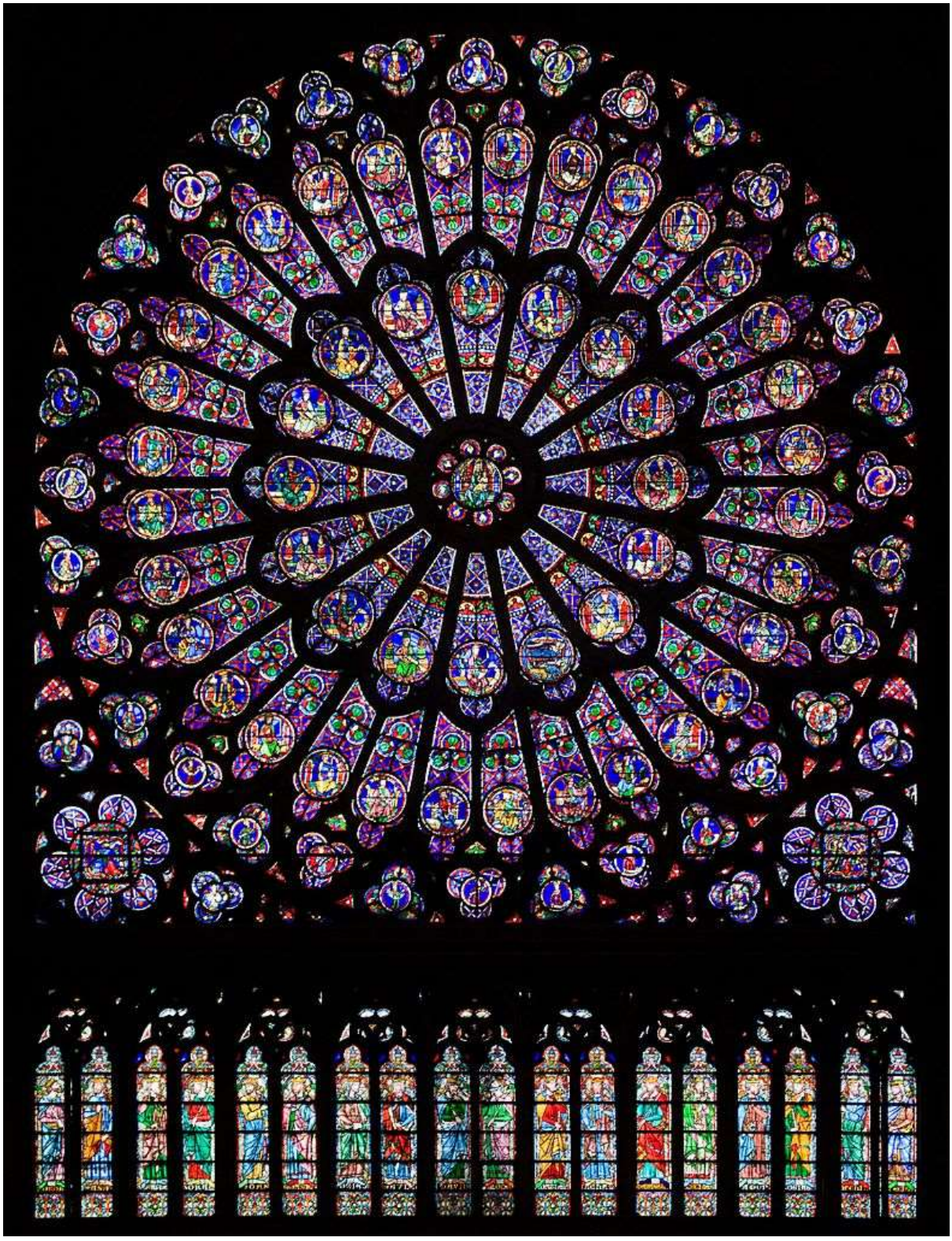
THE NORTHERN HOSPITAL

RIVAROXABAN



North Rose Window, Lead and Stained Glass, 13th Century, Notre Dame Cathedral, Paris.

"It seems to me I see myself dwelling, as it were, in some strange region of the Universe, that neither exists entirely in the slime of the earth nor entirely in the purity of Heaven...by the grace of God, I can be transported from this inferior to that higher world, (in this heavenly light)...The dull mind rises to the truth through material things, and having seen the light (the mind) arises from its former submergence".

Abbott Suger, 1140 A.D

In 1140 A.D the Abbot Suger was emotionally and physically overwhelmed when he finally stepped into his newly renovated brilliantly sun-filled Church of Saint Denis. Arthur Herman explains: "The result was dazzling. When the sunlight poured in through Saint Denis's windows it would cast glowing patterns of blue, red green, and amber gold light against the black of their red frames. Transformed into rainbows of colour, the light streamed and shimmered across the stone floor. If a church's interior should be an image of heaven for the faithful, then entering the Church of Saint Denis meant entering a heaven of light and colour and a radiant external divine proportion".

Although Abbot Suger did not know it at the time, when he stepped into his stunning new light filled church, he had initiated a new oeuvre of Art. One that in contrast to the fleeting new oeuvres that came at went in dizzying succession during the Nineteenth and Twentieth centuries, would last near on three and half centuries until finally supplanted by the Art of the High Renaissance of the late Fifteenth century. Although he merely referred to his creation as "the new style", this style would in later centuries gain the designation of "Gothic Art" this term coined by those of the Renaissance and meant to be derogatory! It referred to the fact that it had evolved from those descendents of the Frankish and Germanic Gothic tribes who during the Dark Ages had destroyed much of Greco-Roman classical Art. The term stuck, but its connotation did not. The Gothic Art of the Dark Ages, is one of the very few magnificent legacies we have from that mysterious period. It was principally an architectural form of Art, whose main purpose was to inspire the illiterate masses to the glories of God. But it did much more than inspire merely the illiterate masses - it inspired great Kings as well. In 1144 the King of France and his queen, Eleanor of Aquitaine attended the official consecration of Saint Denis and they were just as overwhelmed as Abbot Suger had been. Looking up at the great stained glass windows, it seemed as though one was within a vast celestial rainbow - it inspired an emotional wonder just as the first time a small child looks through a kaleidoscope and sees the vision of a heavenly cascading sparkling jewelled Universe.

Gothic Art was a reaction against the previous dark cloistered styles of the Romans and Byzantines, whose vast domed buildings, where, admittedly, full of glorious mosaics, but they had a feeling of suffocating earth bound suppression with their dull candle lit twilight world. The Gothic style aimed to bring in the light of the celestial Heavens and by so doing to transport the very souls of the faithful into that realm - to be closer to God himself. The Sens cathedral and Saint Denis were the prototypes of the "new style" - characterised by vast ribbed interior vaults, three part elevations, the famous pointed Gothic arch of the windows, (originally borrowed from the Islamic world), but above all the dazzling jewels in the crown were the truly monumental, magnificent awe inspiring rose windows. It is difficult therefore for those of the Twenty First century to understand why we do not know the names of the builders, architects and engineers who built the great cathedrals of the Dark and Middle Ages. But this is to completely misunderstand the medieval mind. In contrast to our own celebrity and "star" obsessed world, the builders

of the cathedrals were humble and God fearing. No work was undertaken for personal glory - only for the glory of God. Those who actually built the cathedrals were utterly irrelevant - only the end result that proclaimed God's glory mattered. And unlike today's deadline obsessed world that throws up a skyscraper in just a few years, the great cathedrals were built over many generations spanning hundreds of years! The project itself was a work done for God, lovingly handed down from generation to generation until one day, whenever distant day that might be, it would finally be finished.

To understand the medieval mind we must look to the magisterial William Manchester in his "A World Lit Only By Fire":

"The most baffling, elusive, yet in many ways the most significant dimensions of the medieval mind were invisible and silent. One was the medieval man's total lack of ego. Even those with creative powers had no sense of self. Each of the great soaring medieval cathedrals, our most treasured legacy from that age, required three or four centuries to complete. Canterbury was twenty-three generations in the making; Chartres, a former Druidic center, eighteen generations. Yet we know nothing of the architects or builders. They were glorifying God. To them their identity in this life was irrelevant. Noblemen had surnames, but fewer than one percent of the souls in Christendom were wellborn. Typically, the rest - nearly 60 million Europeans - were known as Hans, Jacques, Sal, Carlos, Will, or Will's wife, Will's son, or Will's daughter. If that was in adequate or confusing, a nickname would do. Because most peasants lived and died without leaving their birthplace, there was seldom need for any tag beyond One-Eye, or Roussie (Redhead), or Bionda (Blondie), or the like.

Their villages were frequently innomimate for the same reason. If war took a man even a short distance from a nameless hamlet, the chances of his returning to it were slight; he could not identify it, and finding his way back alone was virtually impossible. Each hamlet was inbred, isolated, unaware of the world beyond the most familiar landmark; a creek, a mill, or tall tree scarred by lightning. There were no newspapers or magazines to inform the common people of great events; occasional pamphlets might reach them, but they were usually theological and, like the Bible, were always published in Latin, a language they no longer understood. Between 1378 and 1417, Popes Clement VII and Benedict XIII reigned in Avignon, excommunicating Rome's Urban VI, Boniface IX, Innocent VIII, and Gregory XII, who excommunicated them right back. Yet the toiling peasantry was unaware of the estrangement in the Church. Who would have told them? The village priest knew nothing himself; his archbishop had every reason to keep it quiet. The folk were baptized, shriven, attended mass, received the host at communion, married, and received the last rights never dreaming that they should be informed about great events, let alone have any voice in them. Their anonymity approached the absolute. So did their mute acceptance of it...

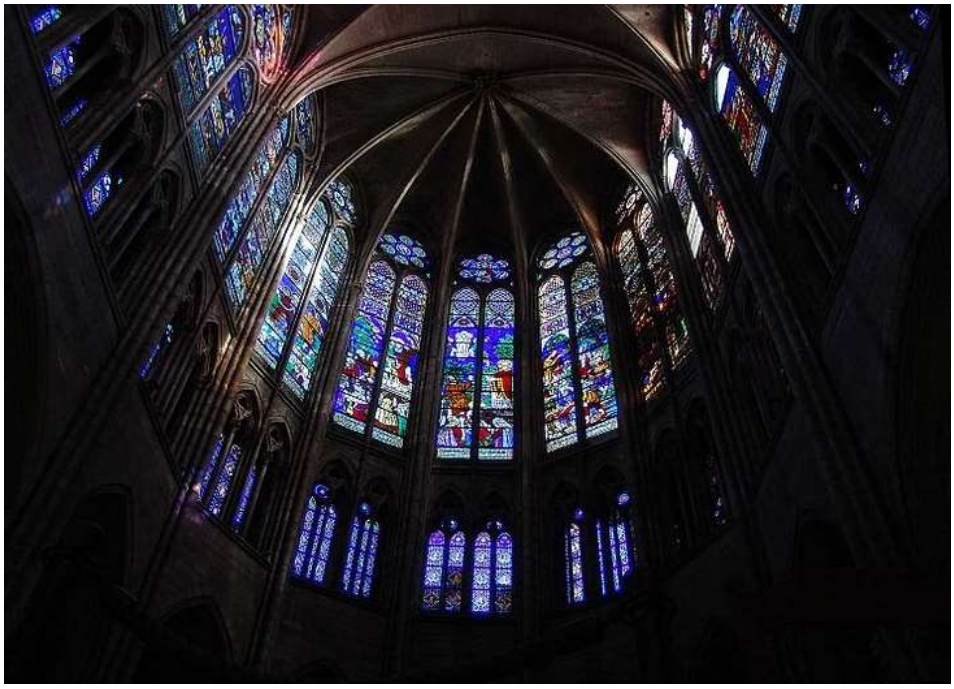
In the medieval mind, there was no awareness of time, which is even more difficult to grasp. In habitants of the (Twenty First century) are instinctively aware of past, present and future. At any given moment most can quickly identify were they are on this temporal scale - the year, usually the date or day of the week, and frequently by glancing at their wrists, the time of day. Medieval men were rarely aware of which century they were living in. There was no reason they should have been....There are very great differences between everyday life in say 1791 and 1991, but there were precious few between 791 and 991.... Any innovation was inconceivable; to suggest the possibility of one would have invited suspicion, and because the accused were guilty until they had proved themselves innocent

by surviving impossible ordeals - by fire - by water or combat to be suspect was to be doomed".

For over three centuries Gothic Art flourished to inspire not only the illiterate masses, but also nobles and even all-powerful Kings and Queens. In the form of the great cathedrals and their truly monumental stained glass miracles, it is one of our most precious legacies from the Dark and Middles Ages. Yet the architects, engineers, and builders, who were clearly very brilliant people, are completely unknown to us today. This is a difficult concept for those of the Twenty first century to appreciate. Today everyone is "famous" for at least Andy Warhol's fifteen minutes. Yet in the millennia to come after us, much of our ephemeral so-called "celebrity" and "fame" will vanish - but Gothic Art will remain eternal for as long as humanity retains some semblance of a soul.

The builders of the medieval cathedrals were unknown brilliant people, dedicated not to themselves but to the greater glory of God. Their purpose was to bring some meaning and noble inspiration to the common people whose lives were mostly nasty, brutal, ignorant and short. The task was patient and unhurried, the banner of the great quest being passed on down through many generations. For the builders, it was not only the end result - but the task itself which gave meaning to their lives.

Today in a more secular world, we still see the fruits of the brilliant but unknown. Astonishing scientific advances continue to improve the lives of the people. Somewhat sadly however the modern motivation, rather than divine, is predominantly the promise of very great profit for the very few. Patience is no longer a well thought of virtue. In the haste to market the NOAC agents, the people are left without a critical antidote in the case of rivaroxaban. At least one consolation however is the hope that the modern "motivation" - will ensure a somewhat more speedy journey than that of a Gothic cathedral to the final end point of a rivaroxaban reversal agent!



The choir of Saint Denis.

RIVAROXABAN

Introduction

Rivaroxaban (trade name in Australia "**Xarelto**"), 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") which is an orally active **direct Factor Xa inhibitor.**

It offers some significant therapeutic advantages over warfarin, but is more problematic with respect to its haemorrhagic complications, as there is **no currently available antidote/ reversal agent.**

Principle differences from dabigatran include:

- Different indications for use
- Different site of action (**direct factor Xa inhibitor** – as opposed to dabigatran which is a direct competitive thrombin inhibitor).
- Different emphasis in laboratory investigations in cases of toxicity.
- **Unlike dabigatran there is no role for dialysis in Rivaroxaban related bleeding.**

See also separate documents on:

- **Rivaroxaban Toxicity (in Toxicology Folder).**
- **Andexanet Alfa (in Drugs folder).**

History

Rivaroxaban was the first clinically used orally active direct factor Xa inhibitor.

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

Rivaroxaban as:

Tablets:

- 10 mg, 15 mg, 20 mg.

Mechanism of Action

Factor Xa acts as an amplifier, generating more than 1000 molecules of thrombin for each molecule of Factor Xa.

Rivaroxaban is an orally active *highly selective* direct **Factor Xa inhibitor.**

By this action Prothrombin is prevented from converting to thrombin, (**see appendix 1 below**).

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

Pharmacodynamics

There is *direct dose* dependent inhibition of **Factor Xa activity**.

Rivaroxaban has a *rapid onset* of action at around 30 minutes.

Its duration of action is around 24 hours.

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.

Disadvantages compared to warfarin:

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

- There is no current specific antidote for drug reversal, (unlike warfarin which has vitamin K and Prothrombin X as its antidotes or heparin which has protamine as its antidote) which makes management of life threatening bleeding problematic.

Rivaroxaban is an orally active direct Factor Xa 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.

Pharmacokinetics

Absorption:

- Rivaroxaban is given orally.

- Bioavailability is 80 - 100 %

- Peak concentrations are reached 3-4 hours following ingestion.

Distribution:

- Plasma protein binding is high, at around 95%.

- The volume of distribution is moderate at about 50 liters.

- It is unknown if rivaroxaban crosses the human placenta.

- Rivaroxaban is excreted in small amounts into human breast milk.

Metabolism and excretion:

- About 1/3 is renally excreted unchanged.

- About 2/3 is metabolised by the liver:

    - ♥ Rivaroxaban is metabolized by the CYP- 3A4 enzyme.

- Half-life is generally around 5 - 9 hours

    - ♥ In the elderly however it is around 11-13 hours.

- ♥ Note that single daily doses of rivaroxaban prolong clotting parameters up to 24 hours, irrespective of the short half-life

Indications

Current indications in Australia include:

1. Treatment of DVT and PE.

2. Prevention of stroke in non-valvular AF

3. Prevention of VTE post elective total hip or total knee replacement.

Contraindications/ Precautions

These include:

1. Renal impairment:

    - For normal or mild impairment (creatinine clearance **> 50 mL/min**), patients can have normal dosing.

    - Moderate renal impairment: ((creatinine clearance **30 - 49 mL/min**). Rivaroxaban dose should be reduced, (generally by 5 mg).

    - Severe renal impairment: (creatinine clearance **< 30 mL/min**). Rivaroxaban is **contraindicated**

2. Do not give with **strong** *inhibitors* of the CYP- 3A4 enzyme: [3]

    - Rivaroxaban is metabolized by CYP3A4 and is a substrate of P-glycoprotein.

    - Its concentration and the risk of bleeding may **increase** if it is given with **inhibitors of CYP3A4** (the manufacturer contraindicates use with **strong** inhibitors of both CYP3A4 and P-glycoprotein, e.g. **azole anti-mycotics** or **HIV protease inhibitors.**

    - Conversely, its concentration and efficacy may be **reduced** if it is given with strong CYP3A4 **inducers**, e.g. St John's Wort.

    - Giving it with a drug that inhibits either CYP3A4 or P-glycoprotein to a **lesser extent**, e.g. clarithromycin, erythromycin, does not have a clinically relevant effect.

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

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

5. Patients with coagulopathies (contraindicated):

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

6. Patients with severe uncontrolled hypertension

7. Patients prone to **recurrent falls.**

8. Patients with known hypersensitivity to the rivaroxaban or to any of the excipients.

9. Patients with significant hepatic impairment:

    - In general terms, those with LFTs 3 times the upper limit of normal and/or a known history of chronic liver disease.

10. Who are pregnant or breastfeeding, (see below):

Pregnancy:

Rivaroxaban is classified as a Class C drug with respect to pregnancy.

Class 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. Specialized texts should be consulted for further details.

From the very limited information available describing the use of rivaroxaban during pregnancy, adverse pregnancy outcomes have not been reported.

However, consider an alternative medicine with more safety information in women who are planning to become pregnant and during pregnancy.

The use of anticoagulants and thrombolytic agents during pregnancy may be associated with an increased risk of placental haemorrhage and subsequent pre-term birth or fetal loss. Consultation with a haematologist for further advice is recommended.

Breast feeding:

Published reports describing the use of rivaroxaban during breastfeeding have not been located. However, small amounts of rivaroxaban are excreted into human breast milk.

Therefore, due to potential severe adverse effects, such as bleeding in the breastfed infant, consider an alternative therapy if possible.

Adverse Effects

1. Bleeding:

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

2. Hypersensitivity reactions, (rare)

Dosing

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

In general terms with **normal renal** function:

Deep vein thrombosis:

Initial treatment of DVT: **15 mg b.d for a period of 3 weeks.**

Then:

Maintenance treatment of DVT: **20 mg daily.**

For prevention of recurrent DVT: **20 mg daily.**

Pulmonary embolism:

Initial treatment of PE: **15 mg b.d for a period of 3 weeks.**

Then:

Maintenance treatment of PE: **20 mg daily.**

For prevention of recurrent PE: **20 mg daily.**

Tablets are taken **with** food.

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

Monitoring:

There are no current readily available laboratory tests that guide therapy with rivaroxaban.

Measurement of the prothrombin time will help determine whether there is any effect of rivaroxaban present, but will **not** accurately predict the **extent** of haemostatic impairment

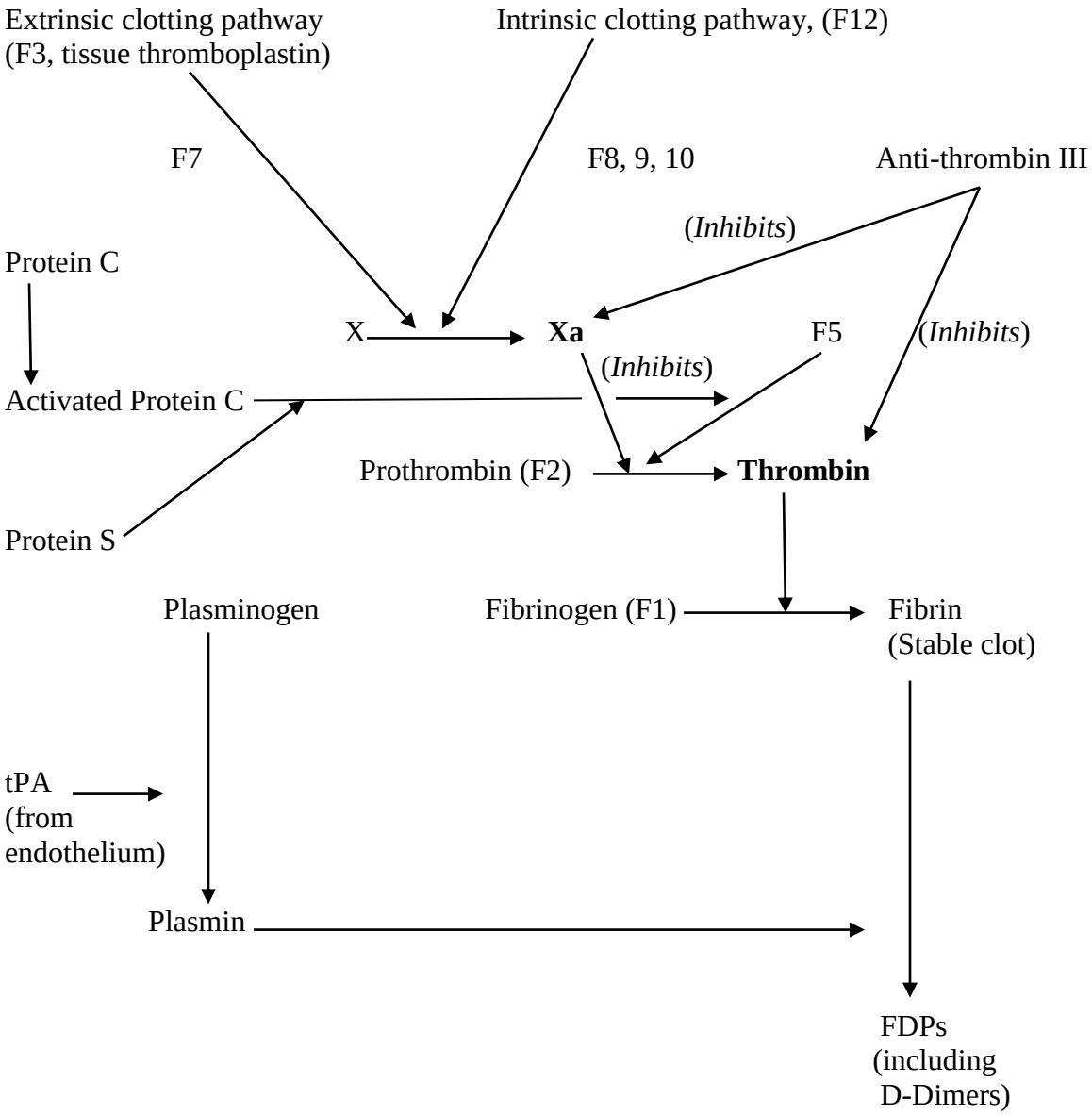
Regular renal function monitoring is recommended, especially for the **elderly.**

Reversal Agent:

There is no currently available specific antidote / reversal agent for rivaroxaban, though work continues on the "decoy" agent Andexanet Alfa.

Appendix 1

The coagulation cascade and fibrinolytic system:



A Transept of St Denis, 12th century; stained glass, Gothic, (Author's photograph, 2017)

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