The Medicines Management Programme considers WARFARIN to be the agent of choice and the first line anticoagulant for most patients with Atrial Fibrillation (1).

The following points should be noted prior to choosing oral anticoagulation:

1) Warfarin is the established anticoagulant of choice for many patients including those with (2):

- **Mechanical heart valves**
- **Valvular atrial fibrillation (AF)**
- **Severe renal impairment**
- **Cancer related venous thromboembolism**
- **Complicated VTE such as patients with recurrent VTE**
- **Patients with antiphospholipid syndrome**

2) Non Vitamin K Oral Anticoagulants (NOACs) *important considerations based on clinical trial evidence*

- The NOACs were not shown to be superior to optimal warfarin therapy in clinical trials for stroke prevention in Atrial Fibrillation i.e. where time in therapeutic range (TTR) for warfarin is over 70% (3,4) (ROCKET-AF: mean TTR = 55% (5), RE-LY: mean TTR = 64% (6), ENGAGE AF-TIMI 48: mean TTR = 68.4% (7), Aristotle: mean TTR = 62% (8))
- The pivotal clinical trial for rivaroxaban in AF was a non-inferiority trial (ROCKET-AF) with a TTR of 55% (5)
- Patients with severe renal dysfunction were excluded from the pivotal clinical trials in AF i.e. exclusion criteria for rivaroxaban in ROCKET-AF: Creatinine Clearance (CrCl) <30ml/min (5), for dabigatran in RE-LY was <30ml/min (6), for edoxaban in ENGAGE AF-TIMI 48 was <30ml/min (7) and for apixaban in Aristotle was <25ml/min (8).

Therefore the Medicines Management Programme advises extreme caution when using NOACs in patients with CrCl of 15-30ml/min. Apixaban, edoxaban and rivaroxaban are contraindicated with CrCl <15ml/min while dabigatran is contraindicated with CrCl <30ml/min.

*Patients on NOAC therapy should have regular assessment of their renal function and have their dose adjusted or therapy reviewed as appropriate (at least 6 monthly review and more frequently if renal impairment or risk factors for impaired renal function)*

- Similar exclusion criteria for renal dysfunction were used in VTE prophylaxis trials and treatment of DVT/PE trials (9,10,11,12,13,14,15,16,17)
- The trials for treatment of DVT/PE with dabigatran and rivaroxaban studied the standard treatment doses only (150mg BD and 20mg once daily respectively). The lower doses of 110mg BD dabigatran and 15mg once daily rivaroxaban to treat DVT/PE have not been studied in a clinical setting (13,15,18,19)
- Trials for the treatment of DVT and PE (for rivaroxaban and dabigatran) were also non-inferiority trials (13,14,15)

3) Significant drug interactions may also occur with NOAC therapy and the most common of these are highlighted in this prescribing aid (18,19,20,21)

4) Poor compliance with NOAC therapies carries a risk of thrombotic events due to the short half life of these agents (18,19,20,21)

5) Reversal agents: an antidote (idarucizumab) is now available for the direct thrombin inhibitor, dabigatran. There is currently no antidote available for the haemorrhagic complications associated with the factor Xa inhibitors.

**WARFARIN DOSING AND MONITORING**


References:

[21] Xarello(rivaroxaban) 2.5mg, 5mg, 10mg fixed tablets SmPC. Last revised August 2013. Accessed at www.medicines.ie on 08/05/14
[22] Eliquis (apixaban) 2.5mg, 5mg fixed film tablets SmPC. Last revised August 2013. Accessed at www.medicines.ie on 29/05/14
[23] Lovenox (rivaroxaban) 10mg, 40mg fixed film SmPC. Date of first authorisation: 19th June 2004. Last updated 24/05/2015. Accessed at www.medicines.ie on 09/05/2015
### Arixiban

**Dosing**
- **Standard dose**
  - Serum creatinine > 133 micromol/L (measured) AND OR weight ≥ 80 kg (Or any two of three above i.e. serum creatinine, age ≥ 80, weight ≤ 80 kg)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Stroke prevention in NVAF</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg twice daily (BD)</td>
<td>2.5 mg BD</td>
<td>this list is not exhaustive; See SmPC for full details</td>
</tr>
<tr>
<td>2.5 mg BD – EXTREME CAUTION, consider alternative (review HAS-BLED and other risk factors)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Contraindicated in CrCl < 15 ml/min**

### Dabigatran

**Dosing**
- **Standard dose**
  - 150 mg twice daily (BD)
  - 100 mg BD (110 mg BD if high bleeding risk)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Stroke prevention in NVAF</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 mg BD</td>
<td>150 mg BD if high bleeding risk</td>
<td>CONTRAINDICATED with other anticoagulants (unless switching, then refer to individual SmPC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CONTRAINDICATED: Ciclosporin, dronedarone, itraconazole, ketoconazole, tacrolimus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AVOID CONCURRENT USE (reduced efficacy): P-gp inducers (e.g. carmustine, phenytoin, rifampicin, St Johns Wort)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CAUTION: P-gp inhibitors (e.g. amiodarone, clarithromycin, quinidine, ticagrelor)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CAUTION (increased bleeding risk): NSAIDs, including aspirin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SSRI/SNRIs – increased risk of bleeding</td>
</tr>
</tbody>
</table>

**Contraindicated in CrCl < 30 ml/min**

**GORD/Gastritis/Oesophagitis**
- **Concomitant Verapamil (take verapamil at the same time as dabigatran)**
  - 110 mg BD

**Eroxaban**

**Dosing**
- **Standard dose**
  - 60 mg once daily

<table>
<thead>
<tr>
<th>Dose</th>
<th>Stroke prevention in NVAF</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 mg once daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CONTRAINDICATED with other anticoagulants (unless switching, then refer to individual SmPC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CAUTION: co-administration of aspirin in elderly patients. The concomitant chronic use of high dose aspirin (&gt;300mg) is not recommended, doses higher than 100 mg should only be performed under medical supervision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CAUTION: P-gp inhibitors – (increased bleeding risk) see dosing guidance opposite for dose reduction recommendations</td>
</tr>
</tbody>
</table>

**Contraindicated in CrCl < 15 ml/min**

**Rivaroxaban**

**Dosing**
- **Standard Dose**
  - 20 mg once daily

<table>
<thead>
<tr>
<th>Dose</th>
<th>Stroke prevention in NVAF</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg once daily</td>
<td></td>
<td>CONTRAINDICATED with other anticoagulants (unless switching, then refer to individual SmPC for guidance)</td>
</tr>
<tr>
<td>15 mg once daily (caution with concomitant medications which increase rivaroxaban plasma concentration)</td>
<td></td>
<td>AVOID CONCURRENT USE (increased bleeding risk): Strong inhibitors of CYP3A4 and P-gp (e.g. itraconazole, ketoconazole, plasmaconazole, HIV protease inhibitors)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AVOID; Dronedarone – (limited clinical data)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CAUTION: Strong inhibitors of CYP3A4 (e.g. clarithromycin) AND renal impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CAUTION (risk of reduced efficacy): Strong inhibitors of CYP3A4 and P-gp (e.g. carmustine, phenytoin, phenobarbital, rifampicin, St Johns Wort)</td>
</tr>
</tbody>
</table>

**Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Not recommended in severe hepatic impairment.**
Discharge prescription (after first diagnosis) should clearly state intended DURATION OF TREATMENT. If rivaroxaban, state how many further days of BD dosing (i.e. 21 days minus number of days doses have already given in hospital) before reducing to once daily and if apixaban, how many further days of 10mg BD before reducing to 5mg BD

### APIXABAN

**DOSING: Treatment of DVT/PE**

**Standard Dose**
- 10mg twice daily for 7 days then reduce to 5mg twice daily for at least 3 months

**CrCl 15-29ml/min**
- No dose adjustment recommended, use with CAUTION

**Prevention of recurrent DVT and PE**
- 2.5mg twice daily. 2.5mg twice daily dose should be started following completion of 6 months treatment with apixaban 5mg twice daily or another anticoagulant. The duration of overall therapy should be individualised after careful assessment of the treatment benefit against the risk of bleeding.

**CONTRAINDICATED in CrCl <15ml/min**

**DABIGATRAN**

**DOSING: Treatment of DVT/PE**

**Standard Dose: Initial treatment with 5 days of parenteral anticoagulant. Then 150mg dabigatran twice daily (BD) for at least 3 months**
- (longer durations determined according to risk factors)

- Less than 75 years (see also options below)
  - 150mg BD

- 75-80 years
  - 150mg BD or if LOW thrombotic risk and HIGH bleeding risk: 110mg BD*

- Over 80 years OR GORD/Gastritis/Oesophagitis OR concomitant Verapamil (take at the same time)
  - 110mg BD NOTE: For DVT/PE the recommendation for the use of 110 mg twice daily is based on pharmacokinetic and pharmacodynamic analyses and has not been studied in this clinical setting.

**CrCl 30ml/min-50ml/min**
- 150mg BD (110mg BD if high bleeding risk)*

**CONTRAINDICATED in CrCl < 30ml/min**

**EDOXABAN**

**DOSING: Treatment of DVT/PE**

**Standard dose: Initial treatment with at least 5 days of parenteral anticoagulant. Then 60mg edoxaban once daily for at least 3 months with longer durations based on permanent risk factors or idiopathic DVT/PE**

Renal impairment (CrCl 15ml/min - 50ml/min) or low body weight (<60kg) or Concomitant use with ciclosporin, dronedarone, erythromycin, ketoconazole (P-gp inhibitors) (based on clinical data)
- 30mg once daily

**CONTRAINDICATED in CrCl < 15ml/min**

**RIVAROXaban**

**DOSING: Treatment of DVT/PE**

**Standard Dose: Initial dose of 15mg twice daily (BD) for first 21 days then reduce to 15mg or 20mg once daily thereafter for at least 3 months (longer durations determined according to risk factors)**

CrCl: 30-49ml/min
- 15mg BD for first 21 days then reduce to 15mg or 20mg once daily thereafter depending on bleeding risk versus risk of recurrent DVT/PE Limited evidence for 15mg dose – based on pharmacokinetic modelling

CrCl: 15-30 ml/min
- EXTREME CAUTION if CrCl < 30ml/min, consider alternative

**CONTRAINDICATED in CrCl<15ml/min**

**Interactions:**
- this list is not exhaustive; See SmPC for full details
- CONTRAINDICATED with other anticoagulants (unless switching, then refer to SmPC)
- AVOID CONCURRENT USE (increased bleeding risk): Strong inhibitors of CYP3A4 and P-gp, such as azole-antimycotics (e.g. ketoconazole, itraconazole, posaconazole, voriconazole) and HIV protease inhibitors (e.g. ritonavir) - check SmPC for more details
- CAUTION (risk of reduced efficacy): Strong inducers of CYP3A4 and P-gp (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St Johns Wort)
- CAUTION (increased bleeding risk): NSAIDs including aspirin
- Antiplalet agents including aspirin will increase risk of bleeding

**NOTE:** Edoxaban is predominately absorbed in the upper gastrointestinal tract. Therefore medicines or disease conditions that increase gastric emptying and gut motility may reduce edoxaban dissolution and absorption. Can be taken with or without food.

**Interactions:**
- this list is not exhaustive; See SmPC for full details
- CONTRAINDICATED with other anticoagulants (unless switching, then refer to individual SmPC)
- AVOID CONCURRENT USE (increased bleeding risk): Strong inhibitors of CYP3A4 and P-gp (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, HIV protease inhibitors).
- Dronedarone – (limited clinical data)
- CAUTION: Strong inhibitors of CYP3A4 (e.g. clarithromycin) AND renal impairment
- CAUTION: Strong inducers of CYP3A4 and P-gp (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St Johns Wort)
- CAUTION (increased bleeding risk): NSAIDs, platelet aggregation inhibitors including aspirin

**Contraindicated in hepatic impairment or liver disease expected to have any impact on survival. Not recommended in severe hepatic impairment, caution in mild to moderate hepatic impairment.**

**Important information: DO NOT OPEN OR CRUSH CAPSULE**

Blistre Pack : Store in the ORIGINAL PACKAGE in order to protect from moisture - not suitable for Monitored Dosage Systems (MDS)

**Rivaroxaban**

Adjust dose for REFLU, RENAL FUNCTION, GORD, and INTERACTIONS

**DOSING: Treatment of DVT/PE**

**Standard Dose: 110mg twice daily (BD) for at least 6 months treatment with rivaroxaban 5mg twice daily or another anticoagulant. The duration of overall therapy should be individualised after careful assessment of the treatment benefit against the risk of bleeding.**

**Prevention of recurrent DVT and PE**
- 2.5mg twice daily. 2.5mg twice daily dose should be started following completion of 6 months treatment with apixaban 5mg twice daily or another anticoagulant. The duration of overall therapy should be individualised after careful assessment of the treatment benefit against the risk of bleeding.

**CONTRAINDICATED in CrCl <15ml/min**

**DOSING: Treatment of DVT/PE**

**Standard Dose: Initial treatment with at least 5 days of parenteral anticoagulant. Then 150mg dabigatran twice daily (BD) for at least 3 months**

**CrCl 30ml/min-50ml/min**
- 150mg BD (110mg BD if high bleeding risk)*

**CONTRAINDICATED in CrCl < 30ml/min**

**DOSING: Treatment of DVT/PE**

**Standard Dose: Initial treatment with at least 5 days of parenteral anticoagulant. Then 60mg edoxaban once daily for at least 3 months with longer durations based on permanent risk factors or idiopathic DVT/PE**

**Renal impairment (CrCl 15ml/min - 50ml/min) or low body weight (<60kg) or Concomitant use with ciclosporin, dronedarone, erythromycin, ketoconazole (P-gp inhibitors) (based on clinical data)**
- 30mg once daily

**CONTRAINDICATED in CrCl < 15ml/min**

**Rivaroxaban**

Adjust dose for REFLU, RENAL FUNCTION and consider INTERACTIONS

**DOSING: Treatment of DVT/PE**

**Standard Dose: Initial dose of 15mg twice daily (BD) for first 21 days then reduce to 15mg or 20mg once daily thereafter for at least 3 months (longer durations determined according to risk factors)**

**CrCl: 30-49ml/min**
- 15mg BD for first 21 days then reduce to 15mg or 20mg once daily thereafter depending on bleeding risk versus risk of recurrent DVT/PE Limited evidence for 15mg dose – based on pharmacokinetic modelling

**CrCl: 15-30 ml/min**
- EXTREME CAUTION if CrCl < 30ml/min, consider alternative
## Prophylaxis of Thromboembolism in Adult Patients After Elective Total Knee Replacement (TKR) or Total Hip Replacement (THR) Surgery

### General Information

Creatinine Clearance (CrCl) should be measured using Cockcroft-Gault equation (SI units): 

\[
\text{CrCl} = \left( \frac{140 - \text{Age (yrs)}}{72} \right) \times \text{Weight(kg)} \times (1.23 \text{ for males} \times 1.04 \text{ for females}) / \text{Serum Creatinine (μmol/L)}
\]

### Arixablan

<table>
<thead>
<tr>
<th>Adjust dose for AGE, BODY WEIGHT, RENAL FUNCTION, and consider INTERACTIONS</th>
</tr>
</thead>
</table>

#### DOSING

| Standard dose | 2.5mg twice daily for 10-14 days (TKR) or for 32-38 days (THR). Initial dose should be taken 12-24 hours after surgery |

### Contraindicated in CrCl < 15ml/min

#### Dabigatran

<table>
<thead>
<tr>
<th>Adjust dose for AGE, RENAL FUNCTION, GORD, and INTERACTIONS</th>
</tr>
</thead>
</table>

#### DOSING

- **Less than 75 years** (see also options below)  
  - 110mg after surgery* then 220mg **once daily** (TKR: 10 days, THR: 28-35 days)
- **> 75 years (treat with caution)**  
  - 75mg after surgery* then 150mg **once daily** (TKR: 10 days, THR: 28-35 days)

#### Renal Impairment (CrCl 30ml/min-50ml/min) [use Cockcroft-Gault equation (SI units)]  
- 75mg after surgery* then 150mg **once daily** (TKR: 10 days, THR: 28-35 days) – treat with caution

### Contraindicated in CrCl < 30ml/min

#### GORD/Gastritis/Oesophagitis

- No adjustment – dose according to the above recommendations

#### Concomitant P-gp inhibitors i.e. verapamil, amiodarone, quinidine (take these agents at same time as dabigatran)

- 75mg after surgery* then 150mg **once daily** (see also renal impairment)

### Rivaroxaban

<table>
<thead>
<tr>
<th>Adjust dose for RENAL FUNCTION and consider INTERACTIONS</th>
</tr>
</thead>
</table>

#### DOSING

| Standard Dose | 10mg once daily for 14 days (TKR) or for 35 days (THR)** |
| CrCl: 30-49ml/min | No dose adjustment required – 10mg once daily for 14 days (TKR) or 35 days (THR)** |
| CrCl: 15-30 ml/min | Extreme Caution required |

### Contraindicated in CrCl < 15ml/min

**Reference:** SmPC for Eliquis® (apixaban), Pradaxa® (dabigatran) and Xarelto® (rivaroxaban) | Version 1.4 | MMP Feb. 2017