The Medicines Management Programme consider WARFARIN or APIXABAN to be the agents of choice for most patients with Non-Valvular Atrial Fibrillation (NVAF)\(^1\)

**WARFARIN** is an appropriate first-line treatment option for stroke prevention in NVAF when time in therapeutic range (TTR) > 70% and may be considered 1\(^{st}\) line treatment, particularly if there are tolerability issues and/or labile international normalised ratios (INRs) with warfarin.

The following points should be considered prior to prescribing an oral anticoagulant:

1. **Warfarin** is the established anticoagulant of choice for many patients including those with: mechanical heart valves, valvular atrial fibrillation, severe renal impairment, cancer related venous thromboembolism (VTE), complicated VTE such as patients with recurrent VTE, patients with antiphospholipid syndrome\(^2\)
3. **Clinical Trials for DOACs**:
   - The DOACS were not shown to be superior to optimal warfarin therapy in clinical trials for stroke prevention in Atrial Fibrillation i.e. where TTR for warfarin > 70% \(^3,4\) (ROCKET-AF: mean TTR=55\(^%\), RE-LY: mean TTR=64\(^%\), ENGAGE AF-TIMI: mean TTR: 68.4\(^%\), ARISTOTLE: mean TTR= 62\(^%\))
   - The pivotal clinical trial for rivaroxaban for stroke prevention in AF was an non-inferiority trial (ROCKET-AF) with a TTR of 55%
   - Patients with severe renal dysfunction were excluded from the pivotal clinical trials in AF i.e. exclusion criteria for ROCKET-AF (rivaroxaban)\(^5\), RE-LY (dabigatran)\(^6\) and ENGAGE AF-TIMI (edoxaban)\(^7\): Creatinine clearance (CrCl) < 30 ml/min; ARISTOTLE (apixaban) exclusion criteria was CrCl < 25 ml/min\(^8\)
   - Therefore the Medicines Management Programme advises extreme caution when using DOACs in patients with CrCl of 15-30 ml/min. Apixaban, edoxaban and rivaroxaban are contraindicated with CrCl < 15ml/min while dabigatran is contraindicated with CrCl < 30 ml/min

**Patients on DOAC therapy should have regular assessment of their renal function and 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\(^9-17\)
- The trials for treatment of DVT/PE with dabigatran and rivaroxaban studied the standard treatment doses only (150mg BD and 20mg OD respectively). The lower doses of 110mg BD dabigatran and 15mg OD 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 non-inferiority trials\(^13-15\)
4. Significant **drug interactions may occur with DOAC therapy** and the most common of these are highlighted in this prescribing aid\(^18-21\)
5. Poor compliance with DOAC therapies carries a risk of thrombotic events due to the **short half-life of these agents**\(^18-21\)
6. **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.
## Apixaban

### Dosing

**Standard dose**

Serum creatinine > 133 mcM/L (measured) AND/280 yrs OR weight ≤ 60 kg (or any two of three above i.e. serum creatinine, age ≥ 80, weight ≤ 60kg)

<table>
<thead>
<tr>
<th>CrCl 15-29 ml/min (use Cockcroft-Gault equation (SI units))</th>
<th>2.5 mg BD – EXTREME CAUTION, consider alternative (review HAS-BLED and other risk factors)</th>
</tr>
</thead>
</table>

### General Information

Creatinine Clearance (CrCl) should be measured using Cockcroft-Gault equation (SI units): CrCl = (140 – Age (yrs)) x Weight (kg) x constant [1.23 for males & 1.04 for females] / Serum Creatinine (μmol/L)

### Interactions

- **Contraindicated with other anticoagulants (unless switching, then refer to individual 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, phenobarbital, rifampicin, St John’s Wort)
- **CAUTION** (increased bleeding risk): NSAIDs including aspirin
- Antiplatelet agents including aspirin will increase risk of bleeding
- **Contraindicated in patients with hepatic disease** associated with coagulopathy and clinically relevant bleeding risk. Not recommended in severe hepatic impairment.

### Dabigatran

### Dosing

**Standard dose**

<table>
<thead>
<tr>
<th>Over 80 years</th>
<th>110 mg BD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal impairment (CrCl 30 ml/min - 50 ml/min)</td>
<td>150 mg BD (110 mg BD if high bleeding risk)</td>
</tr>
</tbody>
</table>

### General Information

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

### Interactions

- **Contraindicated with other anticoagulants (unless switching, then refer to individual SmPC)**
- **Contraindicated with other anticoagulants (except switching, then refer to individual SmPC)**
- **Avoid concurrent use** (increased bleeding risk): Strong inhibitors of CYP3A4 and P-gp
- **CAUTION** (increased bleeding risk): Strong inhibitors of CYP3A4 and P-gp
- **CAUTION** (increased bleeding risk): NSAIDs, including aspirin
- **SSRIs/SNRIs – increased risk of bleeding**
- **Not recommended in hepatic impairment and contraindicated in hepatic impairment or liver disease that is expected to have any impact on survival.**

### Edoxaban

### Dosing

**Standard dose**

| Over 80 years | 110 mg BD |

### General Information

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

### Interactions

- **CAUTION** (increased bleeding risk): Strong inhibitors of CYP3A4 and P-gp
- **CAUTION** (increased bleeding risk): NSAIDs, including aspirin

### Rivaroxaban

### Dosing

| CrCl: 30-49 ml/min | 15 mg once daily (caution with concomitant medications which increase rivaroxaban plasma concentration) |
| CrCl: 15-30 ml/min | 15 mg once daily – EXTREME CAUTION, consider alternative |

### General Information

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

### Interactions

- **Important information:** 15 mg and 20 mg tablets should be taken WITH FOOD
**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

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

**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 individualized after careful assessment of the treatment benefit against the risk of bleeding.

**DIBATGABIN**

**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)

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

**CONTRAINDICATED with other anticoagulants (unless switching, then refer to SmPC)**

**CONTRAINDICATED**: Ciclosporin, dronedarone, itraconazole, ketoconazole, tacrolimus

**AVOID CONCURRENT USE** (reduced efficacy): P-gp inducers (e.g. carbamazepine, phenytoin, rifampicin, St Johns Wort)

**CAUTION**: P-gp Inhibitors (e.g. amiodarone, clarithromycin, quinidine, ticagrelor)

**Verapamil (P-gp inhibitor) – REDUCE DOSE** of dabigatran (take verapamil and dabigatran at the same time)

**CAUTION (increased bleeding risk)**: NSAIDs, including aspirin

**Contraindicated in patients with hepatic impairment or liver disease expected to have any impact on survival. Not recommended in severe hepatic impairment**

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

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

**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)**

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

**EDOXABAN**

**DOSING**: Treatment of DVT/PE
- **Standard Dose**: Initial dose of 15mg twice daily (BD) for first 21 days then reduce to 10mg once daily thereafter for at least 3 months (longer durations determined according to risk factors)

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

**RIVAROXABAN**

**DOSING**: Treatment of DVT/PE
- **Standard Dose**: Initial treatment with at least 5mg twice daily (BD) for first 21 days then reduce to 10mg or 20mg once daily thereafter depending on bleeding risk versus risk of recurrent DVT/PE Limited evidence for 15mg dose – based on pharmacokinetic modelling

**CONTRAINDICATED in 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): CrCl = (140 – Age (yrs)) x Weight(kg) x constant [1.23 for males & 1.04 for females] / Serum Creatinine (\(\mu\)mol/L)

### Apixaban

<table>
<thead>
<tr>
<th>Adjust dose for AGE, BODY WEIGHT, RENAL FUNCTION, and consider INTERACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DOSING</strong></td>
</tr>
<tr>
<td><strong>Standard dose</strong></td>
</tr>
<tr>
<td><strong>CONTRAINDICATED in CrCl &lt; 15ml/min</strong></td>
</tr>
</tbody>
</table>

### Dabigatran

<table>
<thead>
<tr>
<th>Adjust dose for AGE, RENAL FUNCTION, GORD, and INTERACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DOSING</strong></td>
</tr>
<tr>
<td><strong>Less than 75 years (see also options below)</strong></td>
</tr>
<tr>
<td><strong>&gt; 75 years (treat with caution)</strong></td>
</tr>
<tr>
<td><strong>Renal Impairment (CrCl 30ml/min-50ml/min)</strong></td>
</tr>
</tbody>
</table>

### 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 (treat these agents at same time as dabigatran)
| 75mg after surgery\(^*\) then 150mg **once daily** (see also renal impairment) |

### Moderate renal impairment (CrCl 30-50ml/min) AND on concomitant verapamil
| 75mg after surgery\(^*\) then 75mg **once daily** should be considered |

### Rivaroxaban

<table>
<thead>
<tr>
<th>Adjust dose for RENAL FUNCTION and consider INTERACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DOSING</strong></td>
</tr>
<tr>
<td><strong>Standard Dose</strong></td>
</tr>
<tr>
<td><strong>CrCl: 30-49ml/min</strong></td>
</tr>
<tr>
<td><strong>CrCl: 15-30 ml/min</strong></td>
</tr>
</tbody>
</table>

### CONTRAINDICATED in CrCl < 15ml/min

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**References:** SmPC for Eliquis® (apixaban) Pradaxa® (dabigatran) and Xarelto® (rivaroxaban) 
**Version:** 1.5 
**MMP March 2019**