This briefing paper seeks to provide an easily digestible summary of some of the key issues associated with the new anti-coagulants, dabigatran and rivaroxaban. It is aimed at local decision makers in both primary and secondary care.

**What are they and how do they work?**

Dabigatran and rivaroxaban are 2 new oral anticoagulants for prevention of stroke and systemic embolism in non-valvular AF (and associated risk factors) [1, 2]. Warfarin reduces vitamin K dependent synthesis of a range of clotting factors; the newer drugs act at specific points in the clotting cascade: dabigatran directly inhibits thrombin and rivaroxaban factor Xa.

**What do the studies say?**

The pivotal studies for dabigatran and rivaroxaban are RE-LY and ROCKET-AF respectively [3, 4].

RE-LY was a randomised controlled trial designed to compare two doses of dabigatran (110 mg and 150 mg twice daily) with warfarin in 18,113 people with non-valvular AF (NVAF) and at least one stroke risk factor (mean CHADS2 = 2.1). Comparison between warfarin and dabigatran was not double blind given the need to allow warfarin dose adjustments; comparison between dabigatran doses was double blind. The primary endpoint was a composite of prevention of stroke (ischaemic or haemorrhagic) and systemic embolism. At median two-year follow-up, dabigatran 110 mg was non-inferior to warfarin for the primary endpoint (1.54% per year vs. 1.71% per year respectively, p < 0.001), whilst the higher dose (150 mg twice daily) was found to be statistically superior (1.11% per year vs. 1.71% per year, p < 0.001). For all cause mortality there was no statistically significant difference between the groups; death from vascular causes was statistically significantly lower for dabigatran at the 150 mg dose compared to warfarin (2.28% vs. 2.69% per year, p = 0.04). Gastrointestinal bleeding was reported more often for dabigatran 150mg than warfarin (1.56% vs. 1.07% per year, p < 0.001) [3]. A recent Drugs and Therapeutics Bulletin gives further detail and evaluation of the RE-LY study [5].

ROCKET-AF was a multicentre, double-blind, double-dummy, randomized controlled trial [4]. It compared rivaroxaban 20 mg daily (or 15 mg daily where creatinine clearance was 30–49 mL/minute) with warfarin in 14,264 people with AF and either previous systemic embolism, stroke or TIA, or at least two stroke risk factors (mean CHADS2 = 3.5); again the primary endpoint was a composite of stroke (ischaemic or haemorrhagic) and systemic embolism.

There were a number of pre-specified analyses for the study:

- The primary analysis sought to determine non-inferiority for the primary endpoint for the per protocol population all of whom had received at least 1 dose of study drug (13,962 subjects: 6,958 rivaroxaban, 7,004 warfarin; dropout rate < 3%).
- If non-inferiority was achieved, the protocol directed toward a test for superiority in a safety population (14,143 subjects: 7,061 rivaroxaban, 7,082 warfarin).
- A sensitivity analysis was also performed, testing non-inferiority and superiority in the intention-to-treat population (14,171 subjects: 7,081 rivaroxaban, 7,090 warfarin; 93 patients excluded because of violations in good clinical practice guidelines).

Results were as follows:

- For the per-protocol population the primary endpoint occurred at a rate of 1.7% per year for rivaroxaban and 2.2% per year for warfarin, with non-inferiority demonstrated (HR 0.79, 95% CI 0.66–0.96; p < 0.001 for non-inferiority).
• The subsequent safety population analysis indicated that rivaroxaban was superior to warfarin (HR 0.79, 95% CI 0.65–0.95; p < 0.02 for superiority).

• However, whilst the intention-to-treat analysis continued to demonstrate non-inferiority, it did not confirm superiority (HR 0.88, 95% CI 0.75–1.03; p < 0.001 for non-inferiority, p = 0.12 for superiority).

An analysis of safety was also performed:

• For major and non-major clinically relevant bleeding, the event rate was 14.9% for rivaroxaban and 14.5% for warfarin (HR 1.03, 95% CI 0.96–1.11; p = 0.44). Intracranial haemorrhage occurred less frequently with rivaroxaban (0.5% vs. 0.7% per year, p = 0.02), as did fatal bleeding (0.2% vs. 0.5% per year, p = 0.003). Major GI bleeding was more common for rivaroxaban compared to warfarin (3.2% vs. 2.2%, p ≤ 0.001).

Is it possible to compare the two drugs?

There is no specific data or guidance indicating how to choose between dabigatran or rivaroxaban in place of warfarin, and it is unlikely such will become available. The FDA Advisory Committee has suggested that rivaroxaban might be used in patients who have an inadequate response to or cannot take dabigatran or warfarin [6]. The ROCKET-AF and RE-LY trials had different methodologies (see above) with the results reported in different ways such that they cannot be directly compared [3, 4]. We can, however, make some general interpretation and comment with reference to the evidence base for each drug.

Overall, the evidence for both is consistent with suggestion that they are non-inferior to warfarin [3-5, 7]. There is also suggestion of moderate superiority for both drugs; however, for dabigatran this applies only to 150 mg twice daily, whilst for rivaroxaban such was shown only in the per-protocol and safety analyses (which may over emphasise effectiveness) and not for the full intention-to-treat population. For dabigatran, use of the higher dose is contra-indicated in elderly patients given the increased bleeding risk; such an effect may also be a concern for other patient groups [8]. There is also preliminary suggestion that dabigatran may cause a small increase in absolute risk of MI compared to a number of controls [9]. And the absolute benefits conferred by either drug are comparatively small: for dabigatran 150 mg the NNT to prevent 1 systemic embolism or stroke at 1 year is 167, whilst for rivaroxaban 20 mg the NNT is 200 [3, 4].

Further examination of the efficacy reported for the drugs requires consideration of warfarin effectiveness in practice, as determined by time in therapeutic range (TTR). For the small number of UK patients included in RE-LY the average TTR for warfarin was 72% [10]; other UK studies have estimated TTR as being between 52% and 75%, with suggestion that overall UK patients may enjoy comparatively good TTR internationally [11, 12]. The average TTR in RE-LY was 64% and 55% in ROCKET-AF [3, 4]. The generalisability of the results for both studies therefore requires consideration. TTR was calculated slightly differently for each trial, but, crucially, pre-specified analyses examining the results by TTR quartile suggested effectiveness across a range for either drug [10, 13]. However, given that effectiveness is non-uniform when examined by TTR quartile, it is suggested by some that the newer anti-coagulants may be more suitable for those with poorer baseline INR control. General consensus currently suggests that use of either drug should be restricted in relation to prior and current warfarin use.

Whilst summarising clinical differences is not straightforward, a summary of pharmacokinetic and pharmacodynamic properties is possible:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dabigatran etexilate</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodrug</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>~6.5%</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>Half life</td>
<td>12-17 hours</td>
<td>9-13 hours</td>
</tr>
<tr>
<td>Maximum plasma concentration</td>
<td>2 hours</td>
<td>2.5-4 hours</td>
</tr>
<tr>
<td>Protein binding</td>
<td>35%</td>
<td>90%</td>
</tr>
<tr>
<td>Renal excretion</td>
<td>85%</td>
<td>56%</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>P-glycoprotein pump inhibitors / inducers</td>
<td>CYP3A4; P-glycoprotein pump inhibitors / inducers</td>
</tr>
</tbody>
</table>
What are the practical clinical issues?

**Antidotes, drug interactions, and renal impairment**

- Despite their relatively short half-lives, a significant concern for both drugs is the lack of an antidote with potentially serious consequences should a patient present with life threatening haemorrhage or require emergency surgery [7].
- Whilst the lack of the need to monitor therapy has advantages, it may also create potential problems: the ability to objectively measure anticoagulation and determine adherence is lost and any currently unknown drug interactions will be hard to assess with potentially serious consequences [11].
- Both dabigatran and rivaroxaban require dose adjustment in renal impairment, and are contraindicated where there is severe impairment. Prescribers should check renal function prior to initiation and follow the prescribing guidance present on summaries of product characteristics and the BNF [1,2].

**Adherence with therapy**

- Rivaroxaban is taken once daily and dabigatran twice daily. There is no worthwhile or significant difference in levels of compliance between once daily and twice daily regimens, and even highly motivated patients can forget once daily treatment [14]. Some patients require a compliance aid to help them to remember their medicines – dabigatran capsules are moisture sensitive and must not be removed from their packaging and therefore are not suitable for inclusion in a compliance aid [1].

**What do NICE say?**

**Dabigatran**

The NICE final appraisal determination recommends dabigatran as an option for prevention of stroke and systemic embolism within its licensed indication. Treatment initiation must follow an informed discussion between clinician and patient about risks and benefits in comparison with warfarin; such will necessarily include consideration of an individual’s level of international normalised ratio (INR) control [15].

An appeal has been lodged against the FAD which will be heard in February 2012.

**Rivaroxaban**

The NICE appraisal consultation document for rivaroxaban was published in January 2012. Currently NICE is minded not to recommend rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation; however, the manufacturer of rivaroxaban has been asked to provide revised cost-effectiveness analyses comparing rivaroxaban with warfarin. We await final publication, expected in May 2012 [16].

**What are the commissioner and provider issues, particularly in relation to current anti-coagulation services?**

These new drugs are significantly more expensive than warfarin even when the costs associated with anti-coagulation services are taken into account. Their main advantage is their ability to reduce the impact of monitoring on patients’ lives. But even if a significant switch to newer agents was achievable, the fixed costs associated with the current infrastructure for warfarin are likely to remain for the foreseeable future. It therefore seems very unlikely that these drugs offer anything other than a significant cost-pressure in the short to medium term.

Major anti-coagulant service and pathway re-design is required if these drugs are to be used, with clear delineation of responsibilities between primary and secondary care with reference to prescribing initiation and continuation.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Annual cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Variable depending on INR</td>
<td>~£14 + ~£400 for INR monitoring</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>150mg BD</td>
<td>£920</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>20mg daily</td>
<td>£767 (Cost confirmed by manufacturer Jan 2012)</td>
</tr>
</tbody>
</table>

*Costs from Drug Tariff and MIMS January 2012, INR monitoring cost from NICE Clinical Guideline 36
References

   http://guidance.nice.org.uk/TA/Wave24/18/Consultation/DraftGuidance

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