PostScriptExtra

NHS Greater Glasgow and Clyde

# NEW ORAL ANTICOAGULANTS

No. 20, Oct 2012 ◆ Produced by NHS Greater Glasgow and Clyde Medicines Information Service

- There are three new oral anticoagulants licensed in the UK, rivaroxaban, dabigatran and apixaban.
- All three agents are licensed for the prevention of venous thromboembolism (VTE) in hip and knee replacement surgery. Rivaroxaban is the only agent on the total Formulary for this indication.
- Rivaroxaban and dabigatran are licensed for the prevention of stroke and systemic embolism in patients with atrial fibrillation (AF). Both are on the total Formulary for this indication with restrictions.
- In AF, preference of rivaroxaban or dabigatran over warfarin for practical rather than clinical reasons is non-Formulary.
- Rivaroxaban is also licensed for the treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT/pulmonary embolism (PE). It is on the total Formulary as an alternative to warfarin when the intended treatment duration is 3 to 6 months.

## Introduction

There are three new oral anticoagulants licensed in the UK. The direct thrombin inhibitor, dabigatran and the two direct factor Xa inhibitors, rivaroxaban and apixaban.[1] Apixaban is non-Formulary and should not routinely be prescribed in NHS Greater Glasgow & Clyde (NHSGGC).[2] Rivaroxaban and dabigatran are on the Formulary for specific indications and should only be prescribed according to the Formulary restrictions.[2]

***What are the new oral anticoagulants licensed for?***

***Dabigatran*** is the only oral direct thrombin inhibitor currently licensed in the UK.[1] It is licensed for the primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery (THR) or total knee replacement surgery (TKR).[3,4] It is also licensed for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (AF) with one or more risk factors (refer to manufacturer's summary of product characteristics (SPC) for further information).[4,5]

***Rivaroxaban*** is one of two oral direct factor Xa inhibitors currently licensed in the UK.[1] Rivaroxaban is licensed for the prevention of VTE in adult patients undergoing elective THR or TKR.[6] It is also licensed for the prevention of stroke and systemic embolism in adult patients with non-valvular AF with one or more risk factors (refer to SPC for further information) and for the treatment of deep vein thrombosis (DVT), and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults.[7,8]

***Apixaban*** is the other oral direct factor Xa inhibitor currently licensed in the UK.[1] It is licensed for the prevention of VTE in adults who have undergone elective THR or TKR.[9] It is non-Formulary in NHSGGC.[2]

| | Rivaroxaban | Dabigatran | Apixaban |
|---|---|---|---|
| Prevention of VTE following hip or knee replacement surgery | On total Formulary with restrictions | Non-Formulary | Non-Formulary |
| Prevention of stroke and systemic embolism in AF | On total Formulary with restrictions | On total Formulary with restrictions | – |
| Treatment of DVT and prevention of recurrent DVT and PE | On total Formulary with restrictions | – | – |

***NB. New indications for these agents are at different stages of development and therefore they may be licensed for additional indications in the near future.***

## Evidence

### Prevention of VTE following hip and knee replacement surgery

***Rivaroxaban*** is on the total Formulary.[2] ***Dabigatran*** and ***apixaban*** are non-Formulary for this indication because the formulary decision was that the medicines do not represent sufficient added benefit to rivaroxaban, which is already on the Formulary.[2]

***What is the evidence for the use of rivaroxaban for the prevention of VTE following hip and knee replacement surgery?***

Rivaroxaban has only been compared with enoxaparin for this indication. Three randomised, placebo-controlled, double-blind phase III studies compared rivaroxaban 10 mg orally once a day with subcutaneous enoxaparin 40 mg per day (**RECORD 1,2,3**).[10-12] The RECORD study programme involved over 12,500 patients. RECORD 1 and 2 included patients undergoing elective THR surgery [10,11] and RECORD 3 included patients undergoing elective TKR surgery.[12] The primary efficacy outcome in all three studies was the composite of any DVT (symptomatic or asymptomatic), non fatal PE and all-cause mortality. The primary safety outcome was the incidence of major bleeding beginning after the first dose and up to 2 days after the last dose of the study drug (on-treatment period). The studies show that rivaroxaban 10 mg per day was superior to enoxaparin 40 mg daily for the prevention of VTE in patients following THR or TKR and did not show any statistically significant difference in bleeding risk. Refer to PostScript Extra No. 15 for more information.[13]

***What is the evidence for the use of dabigatran for the prevention of VTE following hip and knee replacement surgery?***

Dabigatran has only been compared with enoxaparin for this indication. Dabigatran was shown to be non-inferior to enoxaparin for the prevention of VTE after THR and TKR surgery in the **RE-NOVATE**[14] (n=3494) and **RE-MODEL**[15] (n=2076) studies respectively. Patients were randomised to either dabigatran 150 mg or 220 mg once daily or enoxaparin 40 mg once daily. Both doses of dabigatran were shown to be non-inferior to enoxaparin for the primary efficacy outcome (a composite of total VTE (venographic or symptomatic) and mortality) during treatment in both studies. There was no statistically significant difference in the primary safety outcome of bleeding rates between either dose of dabigatran and enoxaparin in either trial.

***What is the evidence for the use of apixaban for the prevention of VTE following hip and knee replacement surgery?***

Apixaban has only been compared with enoxaparin for this indication. Apixaban was shown to be similar to enoxaparin for the prevention of VTE after TKR and THR surgery in the **ADVANCE-2**[16] (n=3057) and **ADVANCE-3**[17] (n=5407) studies respectively. Patients were randomly allocated to receive apixaban 2.5 mg twice daily or enoxaparin 40 mg once daily. Apixaban was shown to be superior to enoxaparin for the primary outcome, a composite of asymptomatic or symptomatic DVT, non-fatal PE, and all-cause mortality during treatment, in both studies.

There was no statistically significant difference in the primary safety outcome of major or clinically relevant non-major bleeding between apixaban and enoxaparin in either study.

## Prevention of stroke and systemic embolism in AF

***What is the evidence for the use of rivaroxaban for the prevention of stroke and systemic embolism in AF?***

Rivaroxaban has only been compared with warfarin for this indication. Rivaroxaban was shown to be non-inferior to warfarin for the prevention of the primary outcome of stroke and systemic embolism in patients with AF in the double blind **ROCKET-AF** (n=14264) study.[18] The study primarily assessed the non-inferiority of rivaroxaban to warfarin and if non-inferiority was confirmed, tests for superiority were performed. Patients with nonvalvular AF at moderate to high risk of stroke were randomised to receive rivaroxaban 15 mg or 20 mg per day (depending on creatinine clearance) or dose adjusted warfarin (to maintain an INR of 2-3). The median follow up period was approximately two years. In the intention-to-treat (ITT) analysis, the primary end point of stroke or systemic embolism occurred in 2.1% of patients per year in the rivaroxaban group compared to 2.4% of patients per year in the warfarin group (HR, 0.88, 95%CI 0.74-1.03, p<0.001 for non-inferiority, p=0.12 for superiority). Therefore superiority was not demonstrated.

The principal safety endpoint of major and nonmajor clinically relevant bleeding was similar in both groups (HR, 1.03, 95%CI 0.96-1.11, p=0.44). Intracranial haemorrhage and fatal bleeding occurred less frequently with rivaroxaban (0.5% vs. 0.7% per year, p=0.02, 0.2% vs. 0.5% per year, p=0.003 respectively). Major bleeding from a gastrointestinal (GI) site occurred more frequently in the rivaroxaban group (3.2% vs. 2.2%, p<0.001). The rate of adverse effects were similar, except for epistaxis which occurred more frequently in the rivaroxaban group. Patients were only followed up for two years, therefore the long term safety of rivaroxaban is unclear from this study.

***What is the evidence for the use of dabigatran for the prevention of stroke and systemic embolism in AF?***

Dabigatran has only been compared with warfarin for this indication. Dabigatran 150 mg BD was shown to be superior to dose adjusted warfarin for the prevention of stroke or systemic embolism in patients with AF in the **RE-LY** study.[19] Patients (n=18113) with AF with at least one other risk factor for stroke were randomised in a blinded fashion to either dabigatran 110 mg or 150 mg twice daily (BD) or open label, adjusted dose warfarin (to maintain an INR of 2-3). Patients were followed up for a median duration of two years. The primary outcome of stroke or systemic embolism was 1.69% per year in the warfarin group, as compared with 1.53% per year in the group that received dabigatran 110 mg BD (relative risk with dabigatran, 0.91, 95%CI 0.74-1.11, p<0.001 for non-inferiority) and 1.11% per year in the group that received dabigatran 150 mg BD (relative risk, 0.66, 95%CI 0.53-0.82, p<0.001 for superiority). Therefore, dabigatran 110 mg BD was non-inferior to warfarin and dabigatran 150 mg BD was superior to warfarin for the prevention of stroke and systemic embolism.

The primary safety outcome of major bleeding was lower in patients on the lower dose of dabigatran 110 mg BD compared to warfarin and was similar to warfarin in patients receiving dabigatran 150 mg BD (3.36% per year warfarin versus 2.71% dabigatran 110 mg BD (p=0.003) and 3.11% dabigatran 150 mg BD group (p=0.31)).

Although the rate of major bleeding was similar with dabigatran 150 mg BD and warfarin, there was a significantly higher rate of GI bleeding with dabigatran 150 mg BD. Rates of intracranial bleeding were significantly higher in the warfarin group compared to either dose of dabigatran.

In addition to the increased rate of GI bleeding, dabigatran was also associated with an increased risk of dyspepsia compared to warfarin. It has been suggested that the GI effects may be due to acidity from the tartaric acid core of the dabigatran capsules and may have also contributed to the higher discontinuation rates of study drug in the dabigatran groups. There was no difference between dabigatran and warfarin in terms of effects on liver function tests during the study.

The initial results reported a significantly higher rate of myocardial infarction (MI) with patients receiving dabigatran 150 mg BD compared to warfarin. However, a re-analysis of the RE-LY study showed that there was no significant difference in the rate of MI between either dose of dabigatran and warfarin.[20] Patients were only followed up for two years, therefore the long term safety of dabigatran is unclear. The main limitation of the study was its open label nature which has the potential to introduce bias, however, a blinded evaluation of outcome events was undertaken to reduce the possibility of bias.

### Treatment of DVT and prevention of recurrent DVT and PE

***What is the evidence for the use of rivaroxaban for the treatment of DVT and prevention of recurrent DVT and PE?***

Rivaroxaban has only been compared with enoxaparin followed by dose adjusted vitamin K antagonist (VKA) (warfarin or acenocoumarol) for this indication. Rivaroxaban was shown to be non-inferior to enoxaparin-VKA for the prevention of recurrent VTE in the **EINSTEIN-DVT** study.[21] **EINSTEIN-DVT** was a randomised, open label, non-inferiority trial comparing rivaroxaban (15 mg twice daily for three weeks followed by 20 mg once daily) with enoxaparin (1 mg/kg BD) followed by a dose adjusted VKA (either warfarin or acenocoumarol) for 3, 6 or 12 months in 3449 patients with acute, symptomatic DVT. It should be noted that the enoxaparin dose used in the study, 1 mg/kg BD, is higher than the UK licensed dose of 1.5 mg/kg daily for the treatment of VTE.[1] It is uncertain if there are significant implications of this. The primary efficacy outcome of recurrent VTE occurred in 2.1% of the rivaroxaban group versus 3% of patients in the enoxaparin-VKA group (HR, 0.68, 95%CI, 0.44-1.04, p<0.001), therefore, rivaroxaban was non-inferior to enoxaparin-VKA.

The principal safety outcome of major bleeding or clinically relevant non-major bleeding occurred in 8.1% of patients in each group (HR, 0.97, 95%CI, 0.76-1.22, p=0.77). There was no difference in other adverse events between the two groups.

### Treatment of acute PE

***What about the treatment of acute PE, are any of the new agents licensed for this indication?***

None of the new oral anticoagulants are currently licensed for this indication. A licence submission for rivaroxaban has been made to the European Medicines Agency and therefore, it may be licensed for this indication in the near future.[22]

The **EINSTEIN PE** trial showed that ***rivaroxaban*** was non-inferior to standard therapy of enoxaparin followed by VKA for the initial and long term treatment of PE.[23] Patients (n=4832) with acute symptomatic PE with or without DVT were randomised in an open label study to receive either rivaroxaban (15 mg twice daily for three weeks followed by 20 mg once daily) or enoxaparin 1 mg/kg BD followed by adjusted dose VKA (either warfarin or acenocoumarol) for 3, 6 or 12 months. Similarly to the EINSTEIN-DVT study, it should be noted that the enoxaparin dose used in the study, 1 mg/kg BD, is higher than the UK licensed dose of 1.5 mg/kg daily for the treatment of VTE.[1] The primary efficacy outcome of symptomatic recurrent VTE occurred in 2.1% of patients in the rivaroxaban group compared to 1.8% of patients who received standard therapy with enoxaparin and VKA (HR, 1.12, 95%CI, 0.75-1.68, p=0.003 for non-inferiority (p=0.57 for superiority)).
The principal safety outcome of major or clinically relevant non-major bleeding occurred in 10.3% of patients in the rivaroxaban group compared to 11.4% of patients in the standard therapy group (HR, 0.9, 95%CI 0.76-1.07, p=0.23).

## Safety

***What monitoring is required for these agents?*** No blood monitoring is required for any of the new oral anticoagulants and this may be an advantage compared to warfarin. Dabigatran is contraindicated in patients with creatinine clearance (CrCl) < 30 ml/min, therefore, renal function should be assessed in all patients before starting dabigatran and monitored at least once a year in patients older than 75 years or those with a suspected decline in renal function.[24] For rivaroxaban, caution is required in patients with CrCl < 30 ml/min and it is contraindicated when CrCl < 15 ml/min.

***How safe are the new agents and what is the bleeding risk?***

The long term safety of the new oral anticoagulants is currently unknown. Published studies to date show rivaroxaban and dabigatran have a similar overall major bleeding risk to dose-adjusted warfarin and enoxaparin (with the exception of dabigatran 110 mg BD which was associated with less major bleeding than warfarin in patients with AF).[19] A meta-analysis and systematic review of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with AF reported that the new agents were more efficacious for the prevention of stroke and systemic embolism than warfarin and were associated with a significant reduction in the risk for intracranial bleeding (RR 0.49, 95%CI 0.36-0.66).[25] The meta-analysis was inconclusive with respect to major bleeding and GI bleeding due to wide confidence intervals. The risk for MI was similar between the new agents and warfarin (RR 0.96, 95%CI 0.73-1.26).

***What about reversal?***

There is no antidote to any of the agents and this is a major concern. Refer to the Therapeutics handbook and contact your local haematologist for advice on reversal of new anticoagulants.[26]

## Place in Therapy

### Prevention of VTE following hip and knee replacement surgery

***Rivaroxaban*** is on the total formulary restricted to specialist use only in accordance with local protocol.[2] A small proportion of patients may require thromboprophylaxis with rivaroxaban following THR or TKR. In these cases follow orthopaedic and/ or haematology consultant recommendations.[27] Full supply of rivaroxaban is dispensed from the hospital pharmacy.

### Prevention of stroke and systemic embolism in AF

***Dabigatran*** and ***rivaroxaban*** are on the total formulary for this indication restricted to patients currently receiving warfarin who have poor INR control despite evidence that they are complying, patients with allergy or intolerable side effects from coumarin anticoagulants or for patients for whom warfarin has been clinically excluded as a therapeutic option but anticoagulation is deemed safe and appropriate. **Preference over warfarin for practical rather than clinical reasons remains non-Formulary.**[2] Further guidance has been produced by the Heart MCN and is available on StaffNet.

### Treatment of DVT and prevention of recurrent DVT and PE

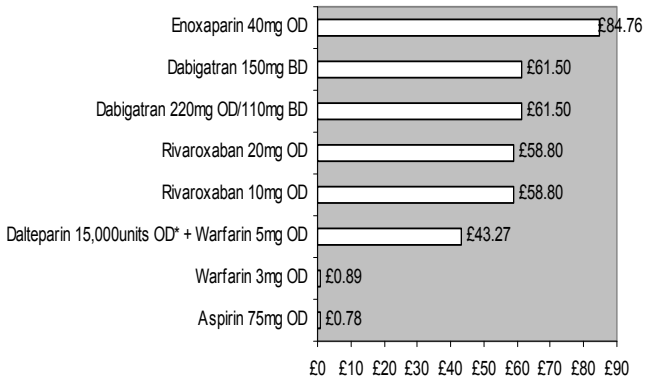
***Rivaroxaban*** is on the total formulary for this indication. It is restricted to use in accordance with local guidance for patients requiring anticoagulation where the intended

duration of treatment is 3 to 6 months. Where indefinite duration is indicated, then the treatment of choice should be a low molecular weight heparin followed by warfarin.[2] The initial 21 days of therapy is dispensed from hospital pharmacy. Further guidance has been produced by the Thrombosis Committee and is available on StaffNet.

## Prescribing advice

Prescribing information can change, therefore, always refer to the latest version of the SPC at http://emc.medicines.org.uk for full information before prescribing any of the new agents. A number of medicines are contraindicated or should be used with caution with rivaroxaban and dabigatran. When prescribing any new medicines for patients currently on a new anticoagulant, always refer to the SPC to check for interactions.

**Cost for 28 days treatment (Scottish drug tariff/eMIMS Sep 2012)**




NB. **Doses shown are for general comparison only and do not imply therapeutic equivalence.** (*Price for dalteparin assumes person weighing 70kg receiving treatment for 5 days)

## References


1. British National Formulary (BNF), No 63, March 2012.
2. NHS Greater Glasgow and Clyde Formulary. Accessed via www.ggcprescribing.org.uk on 10/07/12.
3. Summary of Product Characteristics – Pradaxa® 75mg. Boehringer Ingelheim ltd. Accessed via http://emc.medicines.org.uk on 08/05/12 [last updated on eMC 20/04/12].
4. Summary of Product Characteristics – Pradaxa® 110mg. Boehringer Ingelheim ltd. Accessed via http://emc.medicines.org.uk on 08/05/12 [last updated on eMC 01/05/12].
5. Summary of Product Characteristics – Pradaxa® 150mg. Boehringer Ingelheim. Accessed via http://emc.medicines.org.uk on 08/05/12 [last updated on eMC 30/04/12].
6. Summary of Product Characteristics – Xarelto® 10mg. Bayer plc. Accessed via http://emc.medicines.org.uk on 08/05/12 [last updated on eMC 20/12/11].
7. Summary of Product Characteristics – Xarelto® 15mg. Bayer plc. Accessed via http://emc.medicines.org.uk on 08/05/12 [last updated on eMC 20/12/11].
8. Summary of Product Characteristics – Xarelto® 20mg. Bayer plc. Accessed via http://emc.medicines.org.uk on 08/05/12 [last updated on eMC 20/12/11].
9. Summary of Product Characteristics – Eliquis® 2.5mg. Bristol-Myers Squibb-Pfizer. Accessed via http://emc.medicines.org.uk on 04/05/12 [last updated on eMC 19/09/11].
10. Eriksson BI et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. The New England Journal of Medicine (NEJM) 2008; 358:2765-75.
11. Kakkar AK et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. Lancet 2008; 372:31-39.
12. Lassen MR et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. The New England Journal of Medicine 2008; 358:2776-86.
13. NHS Greater Glasgow and Clyde. PostScript Extra. Rivaroxaban – a new oral anticoagulant, No. 15, Aug 2009. Accessed via www.ggcprescribing.org.uk.
14. Eriksson BI et al. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. Lancet 2007; 370:949-956.
15. Eriksson BI et al. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. Journal of thrombosis and haemostasis 2007; 5:2178-2185.
16. Lassen MR et al. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. Lancet 2010; 375:807-1.
17. Lassen MR et al. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. NEJM 2010; 363:2487-98.
18. Patel MR et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. NEJM 2011; 365:883-91.
19. Connolly SJ et al. Dabigatran versus warfarin in patients with atrial fibrillation. NEJM 2009; 361:1139-51.
20. Connolly SJ et al. Newly identified events in the RE-LY trial. NEJM 2010; 363:1875-6.
21. Bauersachs R et al. Oral rivaroxaban for symptomatic venous thromboembolism. NEJM 2010; 363:2499-510.
22. Bayer AG seeks EU approval for Xarelto for pulmonary embolism 12/04/12. Biospace. Accessed via http://www.biospace.com/News/bayer-ag-seeks-eu-approval-of-xarelto-for/256159/source=TopBreaking.
23. The EINSTEIN-PE investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. NEJM 2012; 366:1287-97.
24. Medicines and Healthcare products Regulatory Agency (MHRA). Drug Safety Update, Vol. 5, Issue 5, Dec 2011. Accessed viahttp://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/index.htm.
25. Miller CS et al. Meta-Analysis of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation. American Journal of Cardiology 2012. Published online http://dx.doi.org/10.1016/j.amjcard.2012.03.049.
26. NHS Greater Glasgow and Clyde. Therapeutics – A Handbook for prescribing in adults 2012.
27. NHS Greater Glasgow and Clyde. Thromboprophylaxis guidelines for orthopaedic patients 2012.