MTRAC
Midlands Therapeutics Review and Advisory Committee

Commissioning Support
Non-vitamin K antagonist oral anticoagulants (NOACs)

Apixaban (Eliquis®), Dabigatran (Pradaxa®), Edoxaban (Lixiana®▼), Rivaroxaban (Xarelto®▼)

Venous thromboembolism: treatment and prevention of recurrence

Considerations for Commissioners:

It was the opinion of the committee that Commissioners may wish to consider the following points:

- Ensure that local trusts have robust treatment pathways/procedures for timely diagnosis and treatment of venous thromboembolism (VTE: deep vein thrombosis [DVT] or pulmonary embolism [PE]) as described in the NICE clinical guideline on venous thromboembolic diseases (CG144; 2015).
- Agree mechanisms for transfer of care (e.g. RiCAD) from secondary to primary care, with the duration of preventative treatment agreed and discussed with the patient at the time of transfer.

Efficacy:

Use of a NOAC (with or without low molecular weight heparin [LMWH] as indicated by the licence] compared with LMWH/warfarin for acute treatment of a confirmed VTE:

- There was no significant difference found between warfarin or NOACs for the incidence of immediate recurrence of a VTE, or VTE-related death in patients treated for a confirmed VTE (see Table 1).[1]
- There was also no significant difference between the NOACs and warfarin for the outcome of all-cause mortality.[1]

Use of a NOAC, warfarin or aspirin for longer-term prevention of a second VTE:

- One trial directly compared a NOAC (dabigatran) with warfarin for the secondary prevention of a VTE (RE-MEDY[2]). The study found dabigatran to be non-inferior to warfarin for the incidence of a recurrent VTE or death associated with VTE (hazard ratio 1.44 [95% confidence interval (CI) 0.78 to 2.64]).[2]
- In The EINSTEIN-CHOICE trial[3], there were fewer recurrent fatal or non-fatal VTEs (or unexplained deaths for which PE could not be ruled out) with rivaroxaban 10 or 20 mg daily treatment *vs*. aspirin as extended treatment. In addition, indirect network meta-analyses of placebo-controlled trials that reported that NOACs (dabigatran, apixaban and rivaroxaban) were likely to have greater efficacy than aspirin in preventing a recurrent VTE, and to be of similar efficacy to warfarin[1].
- All-cause mortality rate was reduced from 0.86% with placebo to 0.41% with NOACs (RR 0.38, 95% CI 0.18 to 0.79, p = 0.009); NNT = 220.[4]

Safety:

- In *acute treatment of a VTE*, the risk of major bleeding and clinically relevant non-major bleeding (CRNMB) was significantly lower with NOAC treatment *vs*. warfarin:
  - Major bleeding (NOACs *vs*. warfarin): 1.08% *vs*. 1.73%; RR 0.63 (95% CI 0.51 to 0.77; p < 0.0001; NNT 155.[1,4]
  - CRNMB: 6.6% *vs*. 8.5%; RR 0.74. 95% CI 0.59 to 0.93, p = 0.01; NNT 52.[1,4]

  (N.B. significant heterogeneity observed for both outcomes)
- For *secondary prevention of a VTE*, CRNMB occurred more often with NOACs than placebo, pooled rates: 4.3% *vs*. 1.8% (RR 2.35, 95% CI 1.65 to 3.35, p < 0.00001).[4] There was no significant difference between NOACs and placebo for major bleeding (0.3% *vs*. 0.19%; RR 1.41 [95% CI 0.53 to 3.76]; p = 0.49).[4]
- In indirect analyses, the risk of major bleeding was lower with apixaban than dabigatran (RR 0.4 [95% CrI 0.19 to 0.81]), edoxaban (RR 0.36 [95% CrI 0.18 to 0.69]) or warfarin (OR 0.3 [0.16 to 0.53])[5]. Results for rivaroxaban and dabigatran were inconsistent across analyses.
- ***Gastrointestinal bleeding***: no significant difference between NOACs and VKA (with or without initial LMWH treatment) in a meta-analysis including seven trials (RR 0.77, 95% CI 0.49–1.21)[6].
- ***Myocardial infarction (MI):*** indirect analyses suggested a higher risk of MI with dabigatran than warfarin and other NOACs.[7] There are no direct head-to-head comparisons of dabigatran with other NOACs for this outcome, and no direct comparisons of NOACs for any of the reported outcomes.

Patient factors:

- All four NOACs are recommended by NICE as options for treatment and secondary prevention of DVT and/or PE (TA341[8], TA327[9], TA354[10], TA261[11] and TA287[12]). The final choice of treatment may depend on an informed discussion with the patient, and other factors such as contraindications to use of warfarin or INR monitoring, the presence of renal or hepatic impairment or the need for prior treatment with a parenteral anticoagulant; see the Summaries of Product Characteristics (SPCs) for full details. To switch between NOACs see notes in the SPCs, or CKS guidance on oral anticoagulation.
- Patients should carry a Patient Alert Card (supplied with all NOACs) in the event of an emergency.
- Dabigatran is the only NOAC for which a licensed reversal agent is available (idarucizumab[13]) for situations requiring emergency surgery, or life-threatening or uncontrolled bleeding. Reversal agents for the remaining NOACs are in clinical development.

Considerations for cost impact:

The estimated incidence of VTE in the general population is 183 per 100,000 people. This equals about 10,455 people in the West Midlands. At current prices, costs for three months' treatment with oral anticoagulants (excluding VAT):

- Warfarin (generic; 7.5mg daily; not including INR monitoring service) £2.98
- Apixaban (Eliquis®; 10 mg twice daily for 7 days, then 5mg twice daily) £186.68
- Dabigatran etexilate (Pradaxa®; 150mg twice daily, following 5 days' treatment with enoxaparin) £193.20
- Edoxaban (Lixiana®▼; 60mg once daily, following 5 days' treatment with enoxaparin) £197.52
- Rivaroxaban (Xarelto®▼; 15 mg twice daily for 3 weeks, then 20mg once daily) £202.05

(Prices updated September 2018)

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Description of the technology

Factor Xa inhibitors and direct thrombin inhibitors have different pharmacodynamic and pharmacokinetic properties, but all act on the final phase of the blood clotting process and represent as a whole the current alternative to vitamin K antagonists (VKAs). Rivaroxaban[14], apixaban[15] and edoxaban[16] directly inhibit activated factor X (factor Xa), a key component of the blood coagulation cascade, inhibiting both the formation and development of blood clots. Dabigatran[17] is a direct inhibitor of thrombin, an enzyme involved in the formation of blood clots. See the individual SPCs for further details of each NOAC.

As initial treatment for an acute VTE, dabigatran (150 mg twice daily) and edoxaban (60 mg once daily) may only be given after an initial period of at least five days' treatment with a parenteral anticoagulant. Apixaban (10 mg twice daily for 7 days, then 5 mg twice daily) and rivaroxaban (15 mg twice daily for 3 weeks, then 20 mg once daily) can be used as single agents.

Clinical evidence for efficacy and safety

The evidence for the efficacy and safety of NOACs compared with warfarin for the acute treatment of VTE and prevention of recurrence of VTE was synthesised in a large health technology assessment (HTA) report[1] and eight further systematic reviews[4,5,18-23]. The main outcomes are summarised, and odds ratios for direct comparisons shown in Table 1 below. Generally, NOACs were non-inferior to warfarin with respect to the treatment and/or prevention of a VTE and had a lower risk of major bleeding. Additional systematic reviews found a higher risk of bleeding complications in women *versus* men[24], and evaluated the effect of extended treatment on mortality[25]. The study found a statistically lower rate of all-cause mortality (RR 0.47, 95% CI 0.29 to 0.75; NNT 102), without significantly greater incidence of major bleeding. Incidences of non-major bleeding were significantly higher with a longer duration of treatment.[25]

Table 1: Summary of key results relating to VTE from the HTA report[1]

Non vitamin-K oral antagonist (NOAC) *(bd = twice daily, od = once daily)*	**Acute treatment**		**Secondary prevention**	
	Odds (95% CI) of symptomatic VTE *vs*. warfarin (INR 2-3)	**Odds (95% CI) of major bleeding (acute VTE) *vs*. warfarin (INR 2-3)**	**Odds (95% CI) of recurrent VTE *vs*. placebo**	**Odds (95% CI) of major bleeding (secondary prevention) *vs*. placebo** *(Imprecise estimates with wide confidence intervals)*
Apixaban (secondary prevention) 2.5 mg bd	-	-	0.17 (0.10 to 0.31)	*0.45 (0.06 to 2.57)*
Apixaban (acute treatment) 5 mg bd (after initial dose of 10 mg twice daily for 7 days)	0.83 (0.58 to 1.18)	0.33 (0.18 to 0.56)	0.18 (0.10 to 0.32)	*0.19 (0.01 to 1.56)*
Dabigatran etexilate: Acute treatment: 150 mg bd following treatment with parenteral anticoagulant for at least 5 days Secondary prevention: 150 mg bd	1.09 (0.75 to 1.58)	0.76 (0.48 to 1.18)	0.08 (0.03 to 0.22) 1.45 (0.80 to 2.60) *vs.* warfarin (INR 2-3)	*6.11 (0.83 to 145)*
Edoxaban tosilate Acute treatment: 60 mg od following treatment with a parenteral anticoagulant for at least 5 days	0.89 (0.70 to 1.13)	0.85 (0.59 to 1.22)	-	-
Rivaroxaban Acute treatment: 20 mg od (after initial dose of 15 mg twice daily for 3 weeks) Secondary prevention: 10 mg od or 20 mg od if high risk of recurrence	0.90 (0.67 to 1.20)	0.55 (0.37 to 0.80)	0.18 (0.09 to 0.37)	*17.8 (1.25 to 8340)*
Warfarin (Dose adjusted to maintain INR 2-3)	-	-	0.05 (0.02 to 0.16)	*12.0 (1.66 to 279)*

INR, international normalized ratio; CI, confidence interval; VTE, venous thromboembolism;

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