InterfacePrescribing & NewTherapies Subgroup

GMMMG Greater Manchester Medicines Management Group NHS

May 2013

Newer Oral Anticoagulants for the prevention of stroke and systemic embolism in adult patients with non valvular AF with one of more risk factors.

The New Therapies Subgroup discussed the above drug at a meeting on 21st May 2013. The recommendation of this subgroup is as follows:*

The New Therapies Subgroup of the GMMMG considered the use of newer oral anticoagulants for the prevention of stroke and systemic embolism in adult patients with non valvular AF with one or more of the following risk factors: previous stroke, TIA or systemic embolism, LVEF < 40%, Symptomatic heart failure ≥ NYHA Class 2, Age ≥ 75yrs, Age ≥ 65yrs with either diabetes mellitus, coronary artery disease or hypertension.

The group recommends the newer oral anticoagulation agents as a treatment option, and should be used in line with NICE TA249, TA256 and TA275

The decision about whether to start treatment with any newer oral anticoagulant should be made after an informed discussion between the clinician and the patient. The discussion should include details around efficacy and safety of each drug compared to warfarin and other NOACS. It must be noted that as new agents limited long term safety data is available.

Further information regarding each individual agent is available on the following pages. Also see updated accompanying protocol.

Review date: May 2015

* Unless superseded by NICE guidance or substantial and significant new evidence becomes available.
▼ Newly marketed drugs and vaccines are intensively monitored for a minimum of two years, in order to confirm the risk/benefit profile of the product. Healthcare professionals are encouraged to report all suspected adverse drug reactions.

Drug	Dabigatran	Rivaroxaban	Apixaban
Clinical Trial Data	The group noted the results from the pivotal RE-LY study which showed that both doses (110mg and 150mg) of Dabigatran were non-inferior to warfarin and that dabigatran 150mg was deemed to be slightly better than warfarin. However it is important to note that the trial was designed to only show non-inferiority so claims of superiority must be interpreted with caution. The group also noted that the 110mg dose was shown to have a slightly lower risk of bleeding than warfarin whilst bleeding risk with the 150mg dose was equivalent to that seen with warfarin therapy. *(n.b taken from original recommendation March 2012 for further information see **NICE TA249**)*	The group noted the results from the pivotal ROCKET – AF study which showed rivaroxaban was non-inferior to warfarin for the prevention of stroke and systemic embolism, and is associated with comparable levels of bleeding. The adverse effect profile is similar to that of warfarin. However the trial population had a higher risk of stroke, as assessed by CHADS2 score, than the target population in the UK. In addition there was a slightly lower proportion of time in therapeutic range in patients on warfarin in ROCKET-AF when compared to normal practice in the UK. (Mean 55% compared to ~65%). *(n.b taken from original recommendation March 2012 for further information see NICE**TA256**)*	The group noted the results from the ARISTOTLE study which showed that apixaban was non-inferior to warfarin for prevention of stroke and systolic embolism in the intention-to-treat population. However it is important to note that the trial was designed to only show non-inferiority so claims of superiority must be interpreted with caution, the difference in the rate of strokes in ARISTOTLE was largely driven by a reduction in haemorrhagic stroke, whereas ischaemic stroke due to embolism is more common in AF. The group also noted that the risk of major bleeds with apixaban was lower than with warfarin. Apixaban was also associated with a lower risk of death from any cause than warfarin, although the statistical significance of this result was borderline. *(n.b taken from original recommendation dec 2012 for further information see NICE **TA275**)*
Mean TTR for warfarin	64%	55%	62%
Mean CHADS2 score	2.1	3.5	2.1
Previous stroke, embolism or TIA	20% (does not include systemic embolism)	55%	19%
Administration	Twice daily	Once Daily	Twice Daily
Half Life	12-14 hours	5-13 hours	12 hours
Cautions (see SPC)	Hepatic impairment http://www.medicines.org.uk/emc/medicine/24839/SPC/Pradaxa+150+mg+hard+capsules/	Hepatic impairment Creatinine clearance 15-29mL/minute http://www.medicines.org.uk/emc/medicine/25586/SPC/Xarelto+20mg+film-coated+tablets	Hepatic impairment creatinine clearance < 15 ml/min, or in patients undergoing dialysis, http://www.medicines.org.uk/emc/medicine/27220/SPC/Eliquis+5+mg+film-coated+tablets
Bleeding (data from trials)	*Major bleeding*: No difference between dabigatran 150 mg BD and warfarin. Less common with dabigatran 110 mg BD than warfarin *GI bleeding*: More common with dabigatran 150 mg BD than warfarin (p=0.0008). No difference	*Major bleeding*: No difference between rivaroxaban and warfarin. *GI bleeding*: More common with rivaroxaban than warfarin (p<0.001) *Intracranial bleeding*: less common with	*Major bleeding*: Less common with apixaban than warfarin (p<0.001) *GI bleeding*: No difference between apixaban and warfarin

	between dabigatran 110 mg BD and warfarin. *Intracranial bleeding*: Less common with both doses of dabigatran than with warfarin (p<0.001). Bleeding risk high in the frail and elderly, particularly with renal impairment and low body weight.	rivaroxaban than warfarin (p=0.02)	*Intracranial bleeding*: Less common with apixaban than warfarin (p<0.001)
When should it be avoided?	AVOID in patients with a history of poor medication adherence. Dabigatran is not stable in compliance aids such as blister packs. Dabigatran is not a suitable alternative to warfarin in patients with bleeding complications associated with warfarin treatment, contraindications to warfarin therapy due to a high bleeding risk, alcohol abuse, and drug overdose.	AVOID in patients with a history of poor medication adherence. Rivaroxaban is not a suitable alternative to warfarin in patients with bleeding complications associated with warfarin treatment, contraindications to warfarin therapy due to a high bleeding risk, alcohol abuse, and drug overdose.	AVOID in patients with a history of poor medication adherence. Apixaban is not a suitable alternative to warfarin in patients with bleeding complications associated with warfarin treatment, contraindications to warfarin therapy due to a high bleeding risk, alcohol abuse, and drug overdose.
Current Acquisition cost per day	£2.20	£2.10	£2.20
Local rebate scheme available	Yes	Yes	No
Points to consider	• In clinical trials, dabigatran 150mg and apixaban were superior to warfarin for the prevention of stroke and systemic embolism. Dabigatran 110mg and rivaroxaban were non-inferior to warfarin. • Similarly, dabigatran 110mg and apixaban were associated with less major bleeding than warfarin. • Each of the NOACs was associated with fewer intra-cranial bleeds than warfarin. • Dabigatran 150mg and rivaroxaban appear to cause more GI bleeds than warfarin, while dabigatran 110mg and apixaban are not significantly different from warfarin. • All three have limited long term safety data. • NOACs have fewer documented interactions than warfarin, but interactions may not be fully characterised and caution is required. • Adherence in practice may be lower than achieved in trials. Without monitoring, adherence may be challenging to assess. • No proven antidotes are available for any of the NOACs. • Generally all three NOACs cost considerably more than warfarin, even when monitoring is taken into account. However in some patients NOACs will be more cost-effective dependent on the time in therapeutic range and their individual monitoring requirements *Reference: New Oral Anticoagulants in Atrial Fibrillation, Medicines in Practice, November 2012; RDTC.*		

This information is a summary to guide prescribers – please consult individual SPCs for further information at www.medicines.org.uk