Guidance on the use of dabigatran▼, rivaroxaban▼, apixaban▼ or edoxaban▼ to prevent thromboembolic events in patients with Atrial Fibrillation (AF)

NHS
Bristol CCG
North Somerset CCG
South Gloucestershire CCG

Does the patient have AF which is not due to heart valve disease and meets NICE TA 249, NICE TA 256, NICE TA 275 or NICE TA 355 criteria for these medications?

NICE TA 249 Criteria – Dabigatran is recommended as an option for the prevention of stroke and systemic embolism for patients who have non valvular AF and at least one of the following:	**NICE TA 256 Criteria – Rivaroxaban is recommended as an option for the prevention of stroke and systemic embolism for patients who have non valvular AF and one or more of the following:**	**NICE TA 275 Criteria – Apixaban is recommended as an option for the prevention of stroke and systemic embolism for patients who have non valvular AF and one or more of the following:**	**NICE TA355 Criteria - Edoxaban is recommended as an option for the prevention of stroke and systemic embolism for patients who have non valvular AF and one or more of the following:**
• Prior stroke or transient ischaemic attack	• Prior stroke or transient ischaemic attack	• Prior stroke or transient ischaemic attack	• Prior stroke or transient ischaemic attack
• Hypertension	• Hypertension	• Hypertension	• Hypertension
• Congestive heart failure	• Congestive heart failure	• Symptomatic heart failure	• Congestive heart failure
• Age 75 years and older	• Age 75 years and older	• Age 75 years and older	• Age 75 years or older
• Diabetes	• Diabetes	• Diabetes	• Diabetes

Priorities for considering a new oral anticoagulant as a treatment option for NICE TA249 / 256 / 275/ 355 identified patient groups

Priority Groups	Patients* with AF with a CHA2DS2-VASc score of 2 or above taking only aspirin or no anticoagulant e.g. patients with a history of a stroke or TIA and meets NICE TA 249 / 256 / 275/ 355 criteria. Take bleeding risk into account.	May be started by primary or secondary care
	Male patients* with AF with a CHA2DS2-VASc score of 1 or above not taking any anticoagulant medication and meets NICE TA 249 / 256 / 275/ 355 criteria	Need to reconsider patients risk / benefit analysis for anticoagulation using GRASP AF audit tool in primary care and CHA2DS2-VASc / HAS-BLED in secondary care.
	On warfarin for AF with poor INR control (Time in Therapeutic Range over the last 6 months < 65%, 2 INR values higher than 5 or 1 value higher than 8 within the past 6 months or 2 INR values less than 1.5 within the past 6 months as per NICE CG 180) and meets NICE TA 249, TA 256, TA 275 or TA 355 criteria	To be identified on GP computer system and / or from anticoagulant clinic. For patients well established on warfarin with Time in Therapeutic Range (TTR) ≥ 65% the benefits of change to dabigatran, edoxaban or rivaroxaban may be minimal (theoretical decrease in risk of intracranial haemorrhage). Apixaban benefits have been shown to be similar across a range of TTR[1], however if patient well controlled on warfarin, changing is not a priority.
	Patients on warfarin with difficulties with INR testing or reliable dosing e.g. fragile skin, dementia and meets NICE TA 249 / 256 / 275 / 355 criteria	In patients with fragile skin / difficult INR testing a NOAC may be a useful option, however dabigatran is not stable out of the foil packaging in a monitored dosage system (MDS) so if required consider rivaroxaban, apixaban or edoxaban.
	Newly diagnosed AF patients meeting NICE TA 249 / 256/ 275/ 355 criteria identified in secondary care e.g. post stroke or TIA	All anticoagulation options including warfarin usually discussed in secondary care and initiated by either primary or secondary care as appropriate.
	Newly diagnosed AF patients meeting NICE TA 249 / 256/ 275/ 355 criteria identified by primary care	All anticoagulation options including warfarin discussed with patients and commenced on diagnosis in primary care

*** This includes patients who have an allergy or intolerance to warfarin or phenindione**

1 Wallentin L, Lopes RD, Hanna M, et al. Efficacy and safety of apixaban compared with warfarin at different levels of predicted INR control for stroke prevention in atrial fibrillation. Circulation. 2013. May 2

All other patients who meet NICE TA 249 or TA 256, TA 275 or TA 355 should be reviewed on a case by case basis

Start

Considerations in prescribing dabigatran▼ , rivaroxaban▼, apixaban▼or edoxaban▼ for the implementation of NICE TA 249, TA 256, TA 275 or TA 355

Is renal function >30ml/min but < 50ml/min or is renal function declining / hard to monitor?	**Is renal function CrCl <30ml/min?**	**Is there hepatic impairment?**	**Is bleeding risk too high to consider warfarin treatment?**	**Is body weight <60kg?**
Apixaban: 5mg b.d. can be used but consider reducing dose if patient has two of the following: age ≥ 80years weight ≤ 60kg serum creatinine ≥ 1.5mg/dL (NB. NICE CG182 recommends apixaban in preference to warfarin in those with an eGFR 30-50ml/min/1.73m^2 with non valvular AF meeting NICE TA275 criteria.)	**Apixaban**: If CrCl < 15ml/min Contraindicated If CrCl 15 – 29 ml/min use with caution and reduce dose to 2.5mg b.d.	**Apixaban:** Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding. Not recommended in severe impairment.	**Apixaban:** Probably *contraindicated*. Check HAS-BLED score* to assess risk, address any modifiable factors. Monitor and reconsider if bleeding risk reduces.	**Apixaban:** 5mg b.d. can be used but consider reducing dose if patient has two of the following: Age ≥ 80years weight ≤ 60kg serum creatinine ≥ 1.5mg/dL
Dabigatran: Standard dose can be prescribed with caution but consider 110mg b.d in those at increased risk of bleeding as moderate renal impairment is a risk factor for bleeding*	**Dabigatran:** *Contraindicated*	**Dabigatran:** Contraindicated if hepatic function is poor enough to threaten life or elevated liver enzymes > 2ULN	**Dabigatran:** Probably contraindicated. Check HAS-BLED score* to assess risk, address any modifiable factors. Monitor and reconsider if bleeding risk reduces.	**Dabigatran:** No adjustments necessary but consider 110mg b.d. as risk factor for increased bleeding.
Edoxaban: Patients with moderate renal impairment should have reduced dose of 30mg o.d. as this is a risk factor for bleeding*	**Edoxaban:** If CrCl < 15ml/min contraindicated. If CrCl 15 – 29ml/min use with caution and reduce dose to 30mg o.d.	**Edoxaban**: Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding. Not recommended in severe impairment.	**Edoxaban:** Probably contraindicated. Check HAS-BLED score* to assess risk, address any modifiable factors. Monitor and reconsider if bleeding risk reduces.	**Edoxaban:** A 30mg once daily dose should be used in those with low body weight less than 60kg.
Rivaroxaban: Patients with moderate renal impairment should have reduced dose of 15mg o.d. as this is a risk factor for bleeding*	**Rivaroxaban**: If CrCl < 15ml/min contraindicated. If CrCl 15 – 29ml/min use with caution and reduce dose to 15mg o.d.	**Rivaroxaban:** *Contraindicated* in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B + C	**Rivaroxaban:** Probably contraindicated. Check HAS-BLED score* to assess risk, address any modifiable factors. Monitor and reconsider if bleeding risk reduces.	**Rivaroxaban:** No dose adjustment needed for extreme weights - if meets licensed indication then 20mg o.d. can be prescribed.

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* HAS – BLED score: http://www.gpnotebook.co.uk/simplepage.cfm?ID=x20110126115649933383&linkID=73899&cook=no&mentor=1
Serum creatinine 1.5mg/dL is approximately equal to 133micromole/L

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Considerations in prescribing dabigatran▼ , rivaroxaban▼ ,apixaban▼or edoxaban▼ for the implementation of NICE TA 249, TA 256, TA 275 or TA 355

Does patient have significant dyspepsia symptoms, suffers gastritis, oesophagitis or gastroesophageal reflux.

No

Is the patient aged 80 years or more?

No

Is the patient aged 75 -80 years with significant gastric co morbidities or high bleeding risk?

No

Is the patient on medicines likely to interact?

No

Consider standard dose:
Apixaban 5mg twice daily*
Dabigatran 150mg twice daily**
Edoxaban 60mg once daily***
Rivaroxaban 20mg once daily****

Yes	Yes	Yes	Yes
Apixaban: 5mg b.d. can be prescribed but careful monitoring for signs and symptoms of bleeding and anaemia is needed.	**Apixaban:** 5mg b.d. can be used but consider reducing dose if patient has two of the following: Age ≥ 80years, weight ≤ 60kg serum creatinine≥ 1.5mg/dL	**Apixaban:** Consider reducing dose if patient has two of the following: Age ≥ 80years weight ≤ 60kg serum creatinine ≥ 1.5mg/dL	**Apixaban:** Concomitant treatment with strong inhibitors of CYP3A4/P-gp e.g. ketoconazole, itraconazole, voriconazole, posaconazole and HIV protease inhibitors are not recommended. Strong inducers of CYP3A4/P-gp e.g. rifampicin carbamazepine, phenobarbital, phenytoin use with caution. Concomitant treatment with any other anticoagulant is contraindicated. For other medicines that should be used with caution or dose adjusted see SPC and BNF for detail.
Dabigatran: Consider a reduced dose of 110mg b.d. and PPI	**Dabigatran:** Only 110mg b.d. is licensed	**Dabigatran:** Consider prescribing 110mg b.d	**Dabigatran:** Concomitant treatment with systemic ketoconazole, ciclosporin, itraconazole, dronedarone and tacrolimus are contraindicated and so dabigatran should be avoided. If taking verapamil, dabigatran 110mg b.d. should be used. Rifampicin, carbamazepine, phenytoin also interact and best avoided. Concomitant treatment with any other anticoagulant is contraindicated. For other medicines that should be used with caution or dose adjusted see SPC and BNF for detail.
Edoxaban: 60mg o.d can be prescribed but careful monitoring for signs and symptoms of bleeding and anaemia is needed.	**Edoxaban:** 60mg o.d can be used if > 80years however dose adjustment may be needed subject to renal function.	**Edoxaban**: No dose adjustment for age but consider reducing dose if patient has moderate or severe renal impairment or low body weight (≤ 60kg)	**Edoxaban:** Concomitant use of edoxaban with ciclosporin, dronedarone, erythromycin, or ketoconazole requires dose reduction to 30 mg once daily. Concomitant use of edoxaban with quinidine, verapamil, or amiodarone does not require dose reduction based on clinical data. . Concomitant treatment with any other anticoagulant is contraindicated. For other medicines that should be used with caution or dose adjusted see SPC and BNF for detail.
Rivaroxaban: 20mg o.d. can be prescribed but careful monitoring for signs and symptoms of bleeding and anaemia is needed	**Rivaroxaban:** 20mg o.d can be used if > 80years however dose adjustment may be needed subject to renal function.	**Rivaroxaban:** No dose adjustment required for age but use with caution in patients with increased bleeding risk. Consider reduced dose where increased bleeding risk.	**Rivaroxaban:** Concomitant treatment with systemic ketoconazole, itraconazole, voriconazole and HIV protease inhibitors is not recommended and so rivaroxaban should be avoided. Rifampicin, carbamazepine, phenobarbital, phenytoin also interact and should be used with caution. Avoid concomitant use of dronedarone. Concomitant treatment with any other anticoagulant is contraindicated. For other medicines that should be used with caution or dose adiusted see SPC and BNF for details

Other considerations:

- Pregnancy – women of child bearing age should avoid pregnancy during treatment with apixaban, dabigatran, edoxaban or rivaroxaban – seek specialist advice
- Breast feeding – seek specialist advice
- Under 18 years – this age is outside the licensed indication – seek specialist advice
- As relatively new, all drugs carry a "black triangle" ▼ and so all suspected adverse reactions should be reported to the MHRA.

** http://www.medicines.org.uk/EMC/medicine/24839/SPC/Pradaxa+150+mg+hard+capsules/
**** http://www.medicines.org.uk/EMC/medicine/25586/SPC/Xarelto+20mg+film-coated+tablets/
* http://www.medicines.org.uk/emc/medicine/27220/SPC/Eliquis+5+mg+film-coated+tablets/
*** https://www.medicines.org.uk/emc/medicine/30506

Serum creatinine 1.5mg/dL is approximately equal to 133micromole/L

ALWAYS REFER TO THE PRODUCT SPC FOR FULL INFORMATION

Indications and contraindications for new oral anticoagulants in non-valvular atrial fibrillation for prevention of stroke

<table>
<tr>
<th>Dabigatran 150mg b.d.</th>
<th>Dabigatran 110 mg b.d.</th>
<th>Rivaroxaban 20mg o.d.</th>
<th>Apixaban 5mg b.d.</th>
<th>Edoxaban 60mg o.d.</th>
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Stable renal function CrCl > 30ml/min without increased risk of bleeding
Normal hepatic function or mild impairment i.e. liver enzymes < 2ULN
Low bleeding risk (see HAS BLED*)
Body weight > 50kg
No significant dyspepsia symptoms, no gastritis, oesophagitis or gastroesophageal reflux
Aged less than 80 years
Aged 75 – 80 years with no significant co –morbidities and low bleeding risk
Not on medication likely to interact with Dabigatran e.g. verapamil

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<td rowspan="2">

Renal function > 30ml/min but < 50 ml/min or renal function declining / hard to monitor - standard dose can be prescribed, consider low dose as moderate renal impairment is a risk factor for bleeding. Also consider other bleeding risk factors.
Weight < 50kg - low weight is a risk factor for bleeding
Significant dyspepsia symptoms, gastritis, oesophagitis or gastroesophageal reflux
Aged 80 years or more
Aged 75 – 80 years with significant gastric co – morbidities or high bleeding risk
Concurrent interacting medication such as verapamil whereby a dose of 110mg b.d. should be used - check BNF for all interactions and assess risk

The addition of a PPI may also be considered to reduce risk of GI related bleeding
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Mild renal impairment (CrCl 50 – 80 ml/min) - no dose adjustment
No dose adjustment for age but always consider renal function
No dose adjustment for weight
Use with caution with interacting medications

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Mild or Moderate renal impairment – no dose adjustment unless fulfils criteria for dose reduction(see below)
Use with caution with interacting medications

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<td>

Mild renal impairment (CrCl of over 50ml/min)
No dose adjustments for age but always consider renal function.
Use with caution with interacting medications

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<tr>
<th>Rivaroxaban 15mg o.d.</th>
<th>Apixaban 2.5mg b.d.</th>
<th>Edoxaban 30mg o.d.</th>
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In moderate and severe renal impairment (CrCl 15 - 49ml/min) reduce dose to 15mg o.d.

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If two of the following criteria are present reduce dose to 2.5mg b.d: Age≥ 80 years, body weight ≤ 60kg or serum creatinine ≥ 1.5mg/dl (133 micromole/L)
Severe renal impairment alone (CrCl 15-29ml/min)

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If one or more of the following is present:
Moderate or severe renal impairment – CrCl 15-50ml/min, low body weight of less than or equal to 60kg, concomitant use of the following P- glycoprotein inhibitors; cyclosporine, dronedarone, erythromycin or ketoconazole.

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Contraindications to Dabigatran 150mg & 110mg	Cautions & possible contraindications to Dabigatran 150mg & 110mg	Contraindications to Rivaroxaban 20mg & 15mg	Cautions & possible contraindications to Rivaroxaban 20mg & 15mg	Contraindications to Apixaban 5mg & 2.5mg	Cautions & possible contraindications to Apixaban 5mg & 2.5mg	Contraindications to Edoxaban 60mg &30mg	Cautions & possible contraindications to Edoxaban 60mg &30mg
• Severe renal impairment (CrCL < 30ml/min) • Hepatic impairment or liver disease expected to impact survival • Clinically significant bleeding • Organic lesion or condition at risk of major bleeding • Hypersensitivity to dabigatran or its excipients • Impairment of haemostasis e.g. genetic clotting disorder • Concomitant treatment with systemic ketoconazole, ciclosporin, itraconazole and tacrolimus – see BNF for full list of interactions • Concomitant treatment with any other anticoagulant (unless switching) • Prosthetic heart valves requiring anticoagulant.	• If bleeding risk too high to consider use of warfarin then dabigatran probably contraindicated as well – check HAS BLED* score to assess risk • Hepatic enzymes >2ULN • Pregnancy – seek specialist advice • Breast feeding – seek specialist advice • Under 18 years – seek specialist advice • Strong CYP3A4 and P-gp inducers e.g. phenytoin, St Johns wort – SPC recommends avoid use.	• Clinically significant bleeding • Lesion or condition at significant risk of major bleeding • Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C • Not recommended in patients with a CrCl<15ml/min • Hypersensitivity to rivaroxaban or its excipients • Pregnancy and breastfeeding • Concomitant treatment with systemic ketoconazole, itraconazole, voriconazole or HIV protease inhibitors – see BNF for full list • Concomitant treatment with any other anticoagulant (unless switching) • Prosthetic heart valves requiring anticoagulant.	• If Bleeding risk too high to consider use of warfarin then rivaroxaban probably contraindicated as well – check HAS BLED* score to assess risk • Under 18 years – seek specialist advice • Strong inducers of both CYP3A4 and P-gp should be co-administered with caution	• Clinically significant active bleeding. • Lesion or condition at significant risk of bleeding. • Hepatic disease associated with coagulopathy and clinically relevant bleeding risk • Not recommended in patients with a CrCl < 15ml/min • Hypersensitivity to apixaban or its excipients • Concomitant treatment with any other anticoagulant (unless switching) • Concomitant treatment with systemic ketoconazole, itraconazole, voriconazole or HIV protease inhibitors – see BNF for full list • Pregnancy and breastfeeding – not recommended • Prosthetic heart valves requiring anticoagulant.	• If bleeding risk too high to consider use of warfarin then apixaban probably contraindicated as well – check HAS BLED* score to assess risk • Under 18 years – seek specialist advice • Strong inducers of both CYP3A4 and P-gp should be co-administered with caution	• Hypersensitivity to the active substance or to any of the excipients. • Clinically significant active bleeding • Hepatic disease associated with coagulopathy and clinically relevant bleeding risk. • Lesion or condition, if considered to be a significant risk for major bleeding. • Uncontrolled severe hypertension • Concomitant treatment with any other anticoagulant • Pregnancy and breast feeding. • Patients with end stage renal disease or on dialysis – not recommended	• If bleeding risk too high to consider use of warfarin then edoxaban probably contraindicated as well – check HAS BLED* score to assess risk • Under 18 years – seek specialist advice

Comparator	Warfarin	Dabigatran 110mg b.d.	Dabigatran 150mg b.d.	Rivaroxaban	Apixaban	Edoxaban
Monitoring	Regular INR tests are needed in order to ensure the correct dose is being used. Monitor for signs of bleeding	No anticoagulation monitoring is needed (therefore unable to check adherence). However, baseline U&Es are needed in all patients prior to initiation & also once a year during continued treatment ,further tests may be required in those aged >75 years or those with suspected decline in renal function. Monitor for signs of bleeding. Also see UKMI guidance on monitoring		No anticoagulation monitoring is needed (therefore unable to check adherence). No requirement in Summary of Product Characteristics (SPC) to do U&Es but it may be useful to review renal function as the dose does need adjusting if renal function declines. Monitor for signs of bleeding. Also see UKMI guidance on monitoring	No anticoagulation monitoring is needed (therefore unable to check adherence). No requirement in Summary of Product Characteristics (SPC) to do U&Es but it may be useful to review renal function as the dose may need adjusting if renal function declines. Monitor for signs of bleeding. SPC recommends liver function tests before initiation. Also see UKMI guidance on monitoring.	No anticoagulation monitoring is needed (therefore unable to check adherence). No requirement in Summary of Product Characteristics (SPC) to do U&Es but it may be useful to review renal function as the dose does need adjusting if renal function declines. Monitor for signs of bleeding. SPC highlights that prior to initiating; liver function testing should be performed. Periodic hepatic monitoring is recommended for patients on edoxaban treatment beyond 1 year.
Antidote for haemorrhage	Vitamin K	No antidote. Supportive care only. As protein binding is low, dabigatran can be dialysed. Lack of national consensus on treating haemorrhage. Consult haematologist		Rivaroxaban is not reversible. Early trial data suggests bleeding effects completely reversed by Prothrombin Complex Concentrate (PCC) (very limited experience). Otherwise, supportive care only. Lack of national consensus on treating haemorrhage. Consult haematologist	Apixaban has no antidote. The initiation of appropriate treatment, e.g. surgical haemostasis or the transfusion of fresh frozen plazma should be considered. The use of activated charcoal may be an option in the management of overdose or accidental ingestion. If bleeding cannot be controlled by these measures, then consider the use of recombinant factor VIIa. Lack of national consensus on treating haemorrhage. Consult haematologist.	No antidote. Management should be individualised according to severity and location of haemorrhage. Appropriate symptomatic treatment as needed e.g. fluid support, blood products. For life threatening bleeding Prothrombin Complex Concentrate (PCC) or recombinant factor VIIa could be considered but limited clinical experience.
Stroke risk		Dabigatran 110mg shown to be non-inferior to warfarin (1.54% vs 1.71% p<0.001 for non-inferiority in RE-LY).	Dabigatran 150mg superior to warfarin (1.11% vs 1.71% p<0.001 for superiority in RE-LY). NNT=167pts would have to be treated for 1 year to get 1 less stroke	Non-inferior to warfarin in ROCKET-AF. The test for superiority in the “as-treated safety population” demonstrated that the p value was significant for rivaroxaban with an event rate for stroke and systemic embolism of 1.7% per year compared with 2.2% per year for warfarin (HR 0.79, 95% CI 0.65 to 0.95, p < 0.02 for superiority).The "Intention To Treat" analysis did not show superiority for rivaroxaban over warfarin	ARISTOTLE showed apixaban to be superior to warfarin, rate of stroke and systemic embolism was 1.27% per year in the apixaban group, compared with 1.60% per year in the warfarin group. (hazard ratio with apixaban, 0.79; 95% CI 0.66 to 0.95; P<0.001 for non-inferiority p=0.01 for superiority)	ENGAGE AF-TIMI 48 showed edoxaban to be superior to warfarin, rate of stroke and systemic embolism was 1.18% per year in the high dose edoxaban group compared to 1.50% warfarin group (HR 0.79 97.5% CI 0.63-0.99 P<0.001 for non-inferiority.)

Bleeding risk	Life threatening bleed / intra cranial bleed & major or minor bleed	Warfarin has a higher risk than dabigatran, rivaroxaban, edoxaban or apixaban	Lower risk for dabigatran (both 110mg and 150mg doses) compared to warfarin. (RE-LY showed intracranial bleeding was lower for dabigatran than warfarin; 0.32% (150mg strength) vs. 0.23% (110mg strength) vs. 0.76% (warfarin) (p<0.001)		Lower risk for rivaroxaban compared to warfarin. Significant reductions of intra-cranial haemorrhage (0.5% vs. 0.7%, p=0.02) & fatal bleeding (0.2% vs. 0.5%, p=0.003)	The ARISTOTLE study showed that apixaban resulted in significantly fewer bleeding events than warfarin for all types of major bleed (rate of intracranial haemorrhage 0.33% for apixaban vs. 0.80% for warfarin, p<0.001[2]).	ENGAGE AF-TIMI 48 showed a lower risk for edoxaban 60mg (0.40% per year) compared to warfarin (0.78% per year) for life threatening bleeding. (p<0.001) It also showed a lower risk for edoxaban than warfarin for any intracranial bleeding (0.39% vs 0.85% per year) (p<0.001).
	Overall major bleed	Warfarin has a higher risk than 110mg dabigatran dose, rivaroxaban, edoxaban and apixaban, same risk as 150mg dabigatran dose	Fewer patients taking dabigatran (110mg) had a major bleed compared to warfarin in the RELY study (2.87% vs. 3.57% (p=0.003)).	Dabigatran (150mg) has the same bleeding risks as warfarin (3.32% vs. 3.57% p=0.31)	No significant difference to warfarin (RE-LY showed 3.6% (rivaroxaban) vs. 3.4% (warfarin) p=0.58). 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)	Apixaban had fewer major bleeding events compared to warfarin (ARTISTOTLE showed 2.13% per year in the apixaban group, as compared with 3.09% per year in the warfarin group (hazard ratio, 0.69; 95% CI, 0.60 to 0.80; P<0.001)	Major bleeding was noted in 2.75% per year of patients taking high dose edoxaban (60mg) compared to 3.43% per year in the warfarin group. These values were significantly lower for the high dose edoxaban group when compared with warfarin (P<0.001)
	Major GI bleeding (Gastritis, oesphagitis GORD)	Warfarin has a lower risk than dabigatran 150mg dose, edoxaban 60mg dose and rivaroxaban, no significant difference with dabigatran 110mg dose or apixaban.	No significant bleeding difference compared to warfarin (1.15% vs. 1.07% p=0.52) in the RE-LY study.	Significantly higher rate with of bleeding with 150mg twice daily dose of dabigatran compared to warfarin (1.56% vs. 1.07%, p = 0.001) in the RE-LY study.	Major bleeding from a GI site was more common in the rivaroxaban group (n=224 events, 3.2%) versus warfarin (154 events, 2.2%)per year p=<0.001 in the ROCKET AF trial	There was no difference in the frequency of gastrointestinal bleeding (including upper/lower GI and rectal bleeding) for apixaban when compared to warfarin in the ARISTOTLE trial (0.76% vs. 0.86% per year, p=0.37[2]).	The rate of GI bleeding was increased in the high dose (60mg) edoxaban group (1.51% per year) when compared to warfarin (1.23% per year) (P=0.03) in the ENGAGE AF-TIMI 48 trial.
Stability		Not suitable for monitored dosage systems (MDS) unless as per NPSA guidance.	Not suitable to go in a standard MDS. The manufacturers of dabigatran have developed a specific box which may be used and is available to order direct from the manufacturers.		Is suitable to go into MDS	Is suitable to go into MDS	Is suitable to go into MDS
GI side effects		Dyspepsia significantly less common than dabigatran	Dyspepsia was the only adverse effect that happened significantly more commonly with both doses of dabigatran compared to warfarin (p<0.001)		No difference to warfarin	No difference to warfarin	Gastrointestinal side effects (diarrhoea, nausea, gastritis and dyspepsia) were reported for a higher proportion of

[2] RDTC, New drug evaluation No 122, Dec 12, Apixaban in atrial fibrillation http://www.nyrdtc.nhs.uk/docs/nde/NDE_122_Apixaban.pdf

							edoxaban subjects than warfarin subjects (6.3% vs 6% for diarrhoea; 3.4% vs. 2.8% for nausea; 2.1% vs. 1.9% for gastritis and 1.8% vs. 1.6% for dyspepsia, respectively).
Hepatic impairment		Monitor INR more frequently	No information available therefore use not recommended if liver enzymes > 2 x upper limit of normal (ULN). Not recommended where hepatic impairment or liver disease is poor enough to threaten life		Contraindicated in hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C	Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Not recommended in patients with severe hepatic impairment. Caution in patients with mild or moderate hepatic impairment (Child Pugh A or B)	Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. It is not recommended in those with severe hepatic impairment. Caution in patients with mild or moderate hepatic impairment. Patients with elevated liver enzymes (ALT/AST > 2 x ULN) or total bilirubin ≥ 1.5 x ULN were excluded in clinical trials. Therefore use with caution in this population. Prior to initiating, liver function testing should be performed.
Renal impairment	CrCl < 30ml/min	If anticoagulation is needed, warfarin may be used in this group of patients with very careful monitoring & specialist advice	Contraindicated	Contraindicated	The SPC states that in patients with severe renal impairment (CrCl < 30ml/min) plasma levels may be significantly increased which may lead to an increased bleeding risk. Use with caution in pts with a CrCl 15 -29ml/min and **reduce the dose to 15mg daily**. Use is **not** recommended in pts with CrCl <15ml/min	Patients with a CrCL of 15 - 29ml/min require **a dose reduction to 2.5mg twice daily.** Use is **not** recommended in patients with CrCl <15ml/min or those undergoing dialysis.	Patients with a CrCl of 15-29ml/min require a **dose reduction to 30mg once daily**. Use is **not** recommended in patients with CrCl <15ml/min or those undergoing dialysis.
	CrCl 30 – 50ml/min	Safe to use	For patients with moderate renal impairment (CrCl 30-50 mL/min) the recommended dose of dabigatran is150 mg twice daily. However, for patients with **high risk of bleeding, a dose reduction to 110 mg twice daily** should be considered. Close clinical surveillance is recommended in patients with renal impairment.		In moderate renal impairment (CrCL 30 - 49ml/min) **reduce the dose to 15mg once daily**	No dose adjustment unless the patient fulfils **criteria for dose reduction** to 2.5mg twice daily based on age, weight and/or serum creatinine. **Note:** NICE CG 182 recommends apixaban for patients with an eGFR of 30-50ml/min/1.73m^2 meeting NICE TA275 criteria	In moderate renal impairment CrCl 30-50ml/minute **reduce the dose to 30mg once daily.**
	CrCl 50 – 80ml/min	Safe to use	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment
		Numerous -	Concomitant treatment with any other anticoagulants is		Concomitant treatment with any other	Concomitant treatment with	Concomitant treatment

Drug interactions Drug interactions continued	well documented	contraindicated. Verapamil, quinine, amiodarone, rifampicin, carbamazepine, St Johns wort, and phenytoin are reported to interact and should be used with caution. Dronedarone, systemic ketoconazole, ciclosporin, itraconazole, tacrolimus and protease inhibitors are contraindicated. See SPC for full list.	anticoagulants is contraindicated. Concomitant use of oral azoles and HIV protease inhibitors are not recommended. Rifampicin, St. John's Wort, phenobarbital, carbamazepine & phenytoin are reported to interact and should be used with caution. See SPC for full list	any other anticoagulants is contraindicated. Azole-antimycotics (e.g. ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (e.g. ritonavir) are not recommended. Rifampicin, phenytoin, carbamazepine, phenobarbital and St John's Wort are reported to interact and should be used with caution. See SPC for full list.	with any other anticoagulants is contraindicated. Concomitant administration with cyclosporine, dronedarone, erythromycin, ketoconazole, resulted in increased plasma concentrations of edoxaban and so requires a dose reduction to 30mg once daily. Concomitant use of quinidine, verapamil or amiodarone does not require dose reduction. Rifampicin, St. John's Wort, phenobarbital, carbamazepine & phenytoin are reported to interact and should be used with caution. See SPC for full list
Prescriber guides and patient alert cards	Yellow warfarin books available http://pcse.england.nhs.uk/supplies/	Available from: https://www.pradaxa.co.uk/patient/af	Available from: http://www.xarelto-info.co.uk/	Available from: https://www.medicines.org.uk/emc/medicine/27220 or https://www.eliquis.co.uk/prescribinginformation/	Available from: https://www.medicines.org.uk/emc/ or http://www.lixiana.co.uk/hcp-resources/

CHA_2DS_2-VASc stroke risk score

C	Congestive Heart Failure/LV dysfunction	1
H	Hypertension	1
A	Age ≥ 75 years	2
D	Diabetes	1
S	Stroke/ TIA/ previous thromboembolism	2
V	Vascular disease (prior MI/peripheral arterial disease/PVD)	1
A	Age 65-74 years	1
Sc	Sex = female	1
Maximum 9 points		

HAS-BLED bleeding risk score

H	Hypertension (SBP >160mmHg)	1
A	Abnormal renal or liver function (1 point each)	1 or 2
S	Previous stroke	2
B	Bleeding history	1
L	Labile INRs (TTR <60%)	1
E	Elderly (age>65yrs)	1
D	Drugs (e.g. aspirin, NSAIDs) or alcohol abuse (1 point each)	1 or 2
Maximum 9 points		