IMPORTANT CLINICAL DIFFERENCES BETWEEN DOACS FOR PATIENTS WITH NVAF

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Below are some clinical considerations in relation to Direct-Acting Oral Anticoagulants (DOACs) use that clinicians/payors may wish to consider before making any large-scale switch/formulary status decisions.

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DOAC TO DOAC SWITCHING

- 2021 European Heart Rhythm Association (EHRA) guidance[1] provide practical guidance on switching between different anticoagulant therapies. It highlights that when switching between different anticoagulant therapies, it is important to ensure the continuation of anticoagulant therapy while minimising the risk for bleeding. This requires insights into the pharmacokinetics and pharmacodynamics of different anticoagulation regimens, interpreted in the context of the individual patient.
- Numerous guidelines highlight the importance of involving the patient in the decision-making process and discussing together the options of anticoagulation is key to adequately assess patients' needs. For example, the NICE AF guideline (NG196)[2] recommends when deciding between anticoagulation treatment options, to discuss the risks and benefits of different drugs with the patient and follow the recommendations on shared decision making in NICE's guideline on patient experience in adult NHS services (NICE CG138).[3]

ARE DOACS CLINICALLY INTERCHANGEABLE?

- All DOACs have been evaluated in large randomised prospective trials and have shown efficacy and safety of the respective agents compared to warfarin[4–7]
- All DOACs are licenced and available for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.[8–11]
- DOACs are not clinically interchangeable.[12] It has been stated before by many commentators that comparisons of DOACs across the phase III clinical trials should not be made because of the heterogeneity of patients' baseline characteristics (see Appendix 1), pharmacokinetic profile of the DOACs (see Appendix 2), and differences in trial designs & outcome definitions.[2,4–7,13–16] With insufficient robust evidence (e.g. head-to-head trials) available to distinguish between the DOACs, there may be significant limitations in making comparisons.
- Furthermore, regarding the update to the NICE AF guidelines (NG196) in April 2021, the NICE committee, based on the evidence and their experience, decided not to recommend one DOAC over the other but instead emphasised that treatment should be tailored to the patient's clinical needs and preferences.[2]
- Each anticoagulant has different risks and benefits that should be considered and fully discussed with the patient as part of informed shared decision making.[2]
- The committee highlighted that the choice might be affected by factors such as renal impairment and swallowing difficulties, and that healthcare professionals should refer to the BNF for advice on contraindications and cautions. They also stressed the importance of adherence and factors that might affect this, such as dosing frequency, when making the decision.[2]

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WHAT ARE THE DIFFERENCES IN CLINICAL EVIDENCE AMONG DOACS IN SPECIFIC NVAF PATIENT POPULATIONS?

Patients with AF and Diabetes

- The prevalence of AF in diabetes, including type 2 diabetes (T2D) is twofold compared to those without diabetes. The presence of T2D in NVAF patients increased their risk of both stroke/systemic embolism and death related to cardiovascular causes compared to those without diabetes. ESC guidelines highlight the importance of including co-morbidities such as diabetes in the holistic management of patients with AF.[17]
- The prevalence of diabetes across the DOAC randomised controlled trials (RCTs) varied from 23%, 25%, 36% and 40% in the dabigatran trial (RE-LY),[7] apixaban trial (ARISTOTLE),[5] edoxaban trial (ENGAGE-AF-TIMI 48)[6] and rivaroxaban trial (ROCKET-AF),[4] respectively.
- All the DOACs were shown to be non-inferior to warfarin in terms of their primary efficacy and safety outcomes in the Phase III clinical trials. Rivaroxaban, dabigatran and edoxaban demonstrated consistent efficacy and safety outcomes vs warfarin in the diabetes sub-groups when compared to their overall respective trial population.[15,18,19] In contrast, while apixaban also demonstrated consistent efficacy outcomes vs warfarin in the diabetes sub-group when compared to the overall trial population, a significant quantitative interaction (p=0.003) was observed between diabetes status and apixaban vs. warfarin demonstrating that the reduction in major bleeding in patients with diabetes compared to warfarin was lower than that for patients without diabetes.[20]
- Among the diabetes sub-groups across the DOAC trials, rivaroxaban demonstrated a significant reduction in vascular death when compared to warfarin.[15] This was also observed in an observational study, RIVA-DM, which analysed electronic health record analysis of patients with NVAF and type 2 diabetes to assess the effectiveness and safety of rivaroxaban (n= 32,078) vs warfarin (n= 83,971) in these patients in routine clinical practice. (HR 0.90; 95% CI 0.86–0.95).[21]

Renal outcomes in anticoagulated AF patients

- AF and chronic kidney disease (CKD) frequently coexist and become more prevalent with advancing age.[22,23]
- Comorbid CKD further increases the risk of thromboembolism as well as the risk of major bleeding and mortality, this can make decisions around anticoagulation more complicated.[24,25]
- Recent observational studies have also shown that NVAF patients treated with DOACs are associated with a significant reduction in the risk of long-term adverse kidney outcomes compared to VKAs.[26–34]
- An observational study in the US (n=9,769) investigated the risk of chronic and acute kidney disease in NVAF patients treated with DOACs compared to warfarin. When compared to warfarin, dabigatran and rivaroxaban were independently associated with a lower incidence of both chronic and acute renal outcomes:
  - Dabigatran:
    - ≥30% decline in estimated glomerular filtration rate (eGFR): 14.29 vs 20.64 events per 100 patient-years; HR 0.72, 95% CI 0.56–0.93, p=0.01
    - Development of acute kidney injury (AKI): 5.93 vs 11.15 events per 100 patient-years; HR 0.55, 95% CI 0.40–0.77, p<0.001
  - Rivaroxaban:
    - Doubling of serum creatinine (SCr): 1.47 vs 3.26 events per 100 patient-years; HR 0.46, 95% CI 0.28–0.75, p<0.01
    - ≥30% decline in eGFR: 15.1 vs 20.64 events per 100 patient-years; HR 0.73, 95% CI 0.62–0.87, p<0.001
    - Development of AKI: 7.63 vs 11.15 events per 100 patient-years; HR 0.69, 95% CI 0.57–0.84, p<0.001

  Apixaban did not show a significant reduction in any renal outcome studied and edoxaban was not assessed.[29]

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WHAT ARE THE DIFFERENCES IN CLINICAL EVIDENCE AMONG DOACS IN SPECIFIC NVAF PATIENT POPULATIONS? cont

Renal outcomes in anticoagulated AF patients – *continued*

- Additionally, a recent UK-based, observational study (n=11,652) also demonstrated a significantly reduced risk of adverse chronic renal outcomes (doubling in SCr: 77.8 vs 128.9 events per 10,000 patient-years; HR 0.63, 95% CI 0.49–0.81, and ≥30% decline in eGFR: 359.8 vs 469.1 events per 10,000 patient-years; HR 0.76, 95% CI 0.67–0.86) in NVAF patients treated with rivaroxaban when compared to warfarin, consistent with other previously reported observational studies.[34]
- This body of observational evidence has influenced guidelines such as the AHA/ACC/HRS Guideline for the management of AF Patients to include a comment on specific DOACs when considering renal function – "Over time, DOACs (particularly dabigatran and rivaroxaban) may be associated with lower risks of adverse renal outcomes than warfarin in patients with AF".[35]
- Renal function decline has been observed in patients with AF treated with oral anticoagulants in many DOAC RCTs.[51–53] The impact of DOACs (vs VKA) on clinically relevant renal dysfunction has not been confirmed due to a lack of renal outcome measures other than eGFR decline in the DOAC RCTs.[29]
- In a prospective real-world study (XARENO), rivaroxaban was associated with reduced risk of adverse kidney outcomes* compared to VKAs (event rates of 8.3 vs. 12.7 respectively, HR: 0.62, CI 95% 0.43-0.88) in patients with NVAF and CKD (eGFR of 15-49 mL/min/1.73m^2). Overall 1455 patients were recruited (median follow-up 2.1 years). Rates of all-cause death were also significantly reduced in patients receiving rivaroxaban vs. VKA (event rates of 17.6 vs. 21.9 respectively, HR: 0.76, CI 95% 0.59-0.98).[55]

*Adverse kidney outcomes were blindly adjudicated and consisted of a composite of eGFR decline to <15mL/min/1.73m^2, need for chronic kidney replacement therapy or development of acute kidney injury

DOACs in advanced age and frailty

- All DOAC RCTs include significant populations of older people (see Appendix 1), often defined as ≥75 years. This varied from 31%, 40%, 40% and 44% in the apixaban trial (ARISTOTLE),[5] dabigatran trial (RE-LY),[16] edoxaban trial (ENGAGE-AF-TIMI 48)[6] and rivaroxaban trial (ROCKET-AF),[4] respectively.
- Stroke outcomes were consistent in the older age sub-groups in those treated with a DOAC compared to VKA.[4–6,16]
- In the dabigatran sub-group analysis, a significant effect of age on increased major bleeding was observed with dabigatran 150mg when compared to warfarin.[16] No age interaction on the rates of major bleeding was seen with apixaban, edoxaban or rivaroxaban vs warfarin in their respective sub-group analyses.[4–6]
- A prospective observational study investigated the effectiveness and safety of rivaroxaban vs VKA in 1,969 individuals with NVAF aged ≥80 years, adjusted for *inter alia*, comorbidities, dementia, and falls. Rivaroxaban was associated with a significant reduction in the risk of major bleeding and intracranial haemorrhage with no difference in the risk of ischaemic stroke when compared to VKA (p<0.0001).[36]
- The EHRA also highlight that "care needs to be taken to minimise the risk of falling and to ensure optimal compliance and adherence".[1]
- AF NICE guidelines state "Do not withold anticoagulation solely because of a person's age or their risk of falls". [2]

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DOACs in NVAF patients with increasing creatinine clearance

- The summary of product characteristics (SmPC) for edoxaban includes the following statement: ”A trend towards decreasing efficacy with increasing CrCl was observed for edoxaban compared to well-managed warfarin ... Edoxaban should be used in patients with NVAF and high CrCl only after a careful evaluation of the individual thromboembolic and bleeding risk”.[9]
- In regard to increasing creatinine clearance, rivaroxaban, apixaban and dabigatran do not have any restrictions in their respective SmPCs (see Appendix 3).[8,10,11]

PRACTICAL CONSIDERATIONS BEFORE INITIATION OF DOACS

The appropriate use of DOACs requires a carefully considered approach to many practical aspects and is provided for by many clinical situations in their respective SmPCs[8–11] and the EHRA practical guide for the use of DOACs in patients with atrial fibrillation.[1] Please refer to Appendix 4 for key differences in the practical considerations when initiating DOACs in NVAF.

Initiation of a medication can be a resource-intensive intervention. Firstly, patients need to be identified and evaluated for their suitability; co-morbidities, concurrent medications, and dosing then also need to be taken into consideration prior to initiation. A consultation with the patient is necessary to discuss the proposed change and any subsequent monitoring required.

Pharmacokinetics and drug–drug interactions of DOACs

- Many patients with AF have multiple comorbidities with subsequent concurrent medications. Approximately 80% of participants with self-reported AF had at least one other co-morbid long-term condition[54]
- Each DOAC has slight variations in their drug-drug interactions which can affect the DOAC plasma levels and subsequently the anticoagulant effect.[1,8–11] The pharmacokinetic interactions of accompanying drugs and comorbidities should be considered when changing medication for a specific patient (see Appendix 5).

Correct Dosing

- All four available DOACs have different dosages with different dose reduction criteria.[8–11] These criteria vary from age, body weight, renal function, and concomitant medications from one DOAC to another.
- Rivaroxaban requires an assessment of renal function, calculated as creatinine clearance via the Cockcroft Gault equation, to determine the correct dose.[8]
- These specific criteria for each DOAC need to be considered when initiating or switching between the DOACs to ensure the patient is prescribed the tested and approved, correct dose to provide optimal benefit for the patient. If dose adjustment requirements are complex this can lead to the potential for dosing errors. Moreover, an awareness of any changes to a patient that would lead to a change in their DOAC dosing is crucial to maintain adequate protection.
- UK observational data from 30,467 patients with NVAF and a first prescription for apixaban, dabigatran or rivaroxaban has suggested that inappropriate DOAC dosing occurs in approximately a fifth of new patients who are eligible for the standard dose.[37]
- The consequences of inappropriate dosing have been highlighted by several observational studies and registries which show an association of higher rates of adverse events in NVAF patients on inappropriate reduced DOAC doses.[38,39]

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PHARMACOKINETICS AND DRUG–DRUG INTERACTIONS OF DOACS cont

Ease of adherence

- Owing to the short half-lives of the DOACs, patient adherence is key in ensuring tolerable and effective anticoagulation.[40]
- Numerous factors have been highlighted that can influence adherence, one of which is frequency of dosing.[41]
- Edoxaban and rivaroxaban are both indicated to be taken once-daily, and apixaban and dabigatran twice-daily in patients with NVAF.[8–11]
- Over 80% of AF patients in two separate adherence studies (80.7%, n=918 and 82.5%, n=274) expressed a preference for once daily (OD) daily dosing,[42,43] with 43% of patients with AF treated with DOACs (n=758) in another study indicating that dosing frequency is the most important attribute for a patient's choice of DOAC.[44]
- Given that patient preference may influence long term adherence[45] and poor adherence to DOACs is linked with high stroke rates, particularly in those with a CHA_2DS_2-VASc score ≥2,[46] frequency of dosing should be considered alongside efficacy and safety when providing a DOAC option to patients with NVAF.

Management of bleeding under DOAC therapy

- Reversal agents are now licenced and available for apixaban, dabigatran & rivaroxaban.[8,10,11] Edoxaban does not have a specific licensed reversal agent[9] (see Appendix 4).
- Idarucizumab is a specific reversal agent licenced for use in adults treated with dabigatran when rapid reversal of its anticoagulant effects is required for emergency surgery or urgent procedures, or in life-threatening or uncontrolled bleeding.[47,48]
- Andexanet alfa is a specific reversal agent licenced and NICE-recommended for use as an option for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding, only if the bleed is in the gastrointestinal tract.[8,11,49,50]

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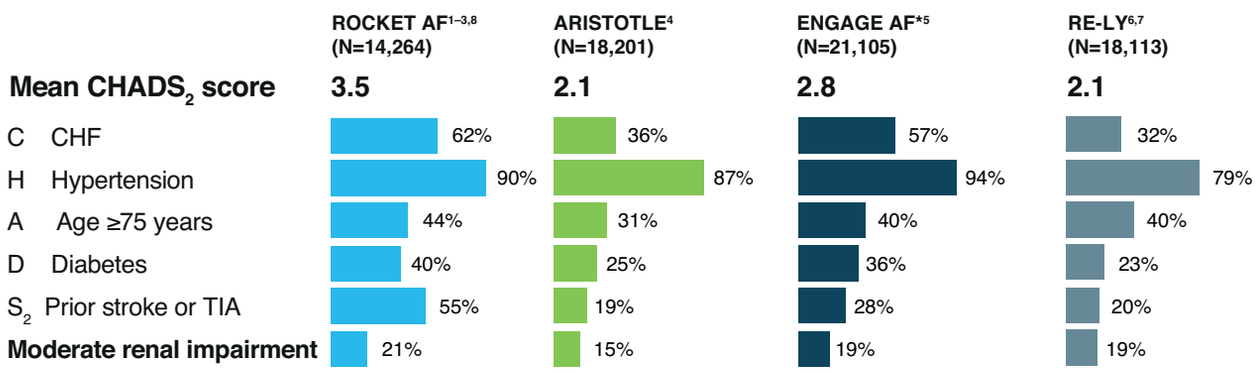
APPENDICES:

Appendix 1: Differences in baseline characteristics of the study participants enrolled onto each DOAC RCT[1–8]



No head-to-head clinical trial comparisons between the DOACs have been performed.

**In ENGAGE AF, the 'low dose edoxaban regime' arm of the study with 7,034 patients does not provide efficacy & safety data to support the licence, so the size of the study population – 'high dose' arm & warfarin arm – which provides the evidence for the licence is 14,071. ROCKET-AF study supporting the licence for rivaroxaban had 14,264 patients.*

AF, atrial fibrillation; CHF, congestive heart failure; DM, diabetes mellitus; DOAC, direct-acting oral anticoagulant; RCT, randomised control trial; TIA, transient ischaemic attack.

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APPENDICES:

Appendix 2: Pharmacokinetic profiles of the four available DOACs

	Apixaban[1]	Dabigatran[2]	Edoxaban[3]	Rivaroxaban[4]
MoA	Activated factor Xa inhibitor	Direct thrombin inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor
Prodrug?	No	Yes	No	No
Oral bioavailability	~50%	6.5%	~62%	80–100%*
Renal clearance	27%	85%	35%	33%
C_{max}	3–4 h	2–6 h†	1–2h	2–4 h
Half-life	~12 h	12–14 h	10–14 h	5–13 h
Fixed dosing (SPAF indication)	BID	BID	OD	OD

BID, twice daily; OD, once daily; SPAF: stroke prevention in atrial fibrillation.
*15 and 20 mg tablets are to be taken with food.
†Postoperative period.

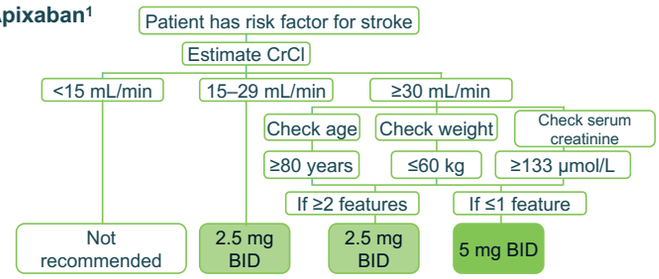
1. Apixaban SmPC; 2. Dabigatran SmPC; 3. Edoxaban SmPC; 4. Rivaroxaban SmPC.

IMPORTANT CLINICAL DIFFERENCES BETWEEN DOACS FOR PATIENTS WITH NVAF

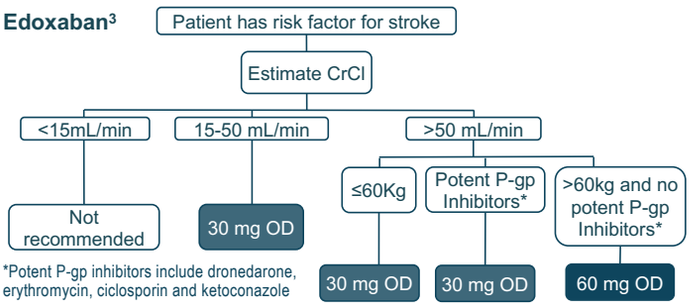
APPENDICES:

Appendix 3: DOAC dosing algorithms for NVAF

Apixaban[1]



Edoxaban[3]

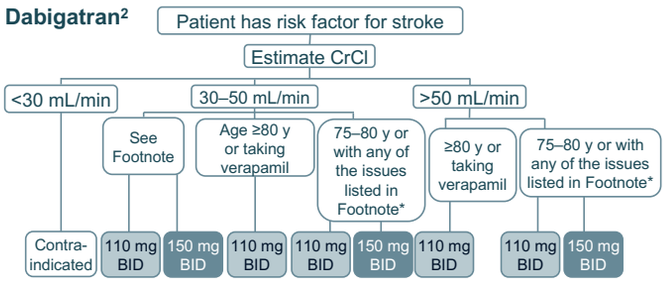


*Potent P-gp inhibitors include dronedarone, erythromycin, ciclosporin and ketoconazole

Please refer to individual DOAC SmPCs for guidance on initiating specific DOACs presented in this slide.

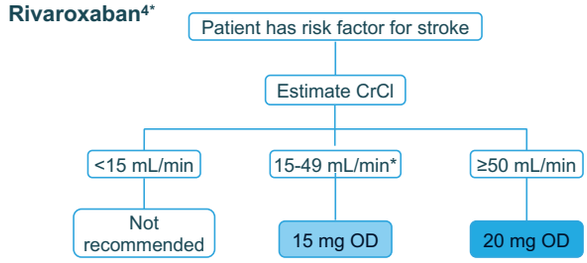
1. Apixaban SmPC; 2. Dabigatran SmPC; 3. Edoxaban SmPC; 4. Rivaroxaban SmPC.

Dabigatran[2]



*Dabigatran dose of 110 mg or 150 mg BID, based on individual assessment of thromboembolic and bleeding risk in patients with gastritis, esophagitis or gastroesophageal reflux, or increased bleeding risk

Rivaroxaban[4*]



*Rivaroxaban to be used with caution in patients with CrCl 15–29 mL/min, and in patients with renal impairment concomitantly receiving other medicinal products that increase rivaroxaban plasma concentrations.

IMPORTANT CLINICAL DIFFERENCES BETWEEN DOACS FOR PATIENTS WITH NVAF

Appendix 4: Key Clinical Differences between DOACs as per SmPC

Key clinical differences as per SMPC	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Indication	Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or TIA.	Prevention of stroke and systemic embolism in adult patients with NVAF, with one or more risk factors, such as prior stroke or TIA; age≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II).	Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or TIA	Prevention of stroke and systemic embolism in adult patients with NVAF, with one or more risk factors, such as prior stroke or TIA; age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension.
Initiation	No specific test	Liver function should be checked	Liver function should be checked. Renal function should be assessed in all patients prior to initiation of treatment with edoxaban.	Renal function should be checked
Method of admin	OD with Food	BID with or without food	OD with or without food	BID with or without food
Dosing adjustments	The recommended dose is 20 mg od. In patients with moderate (CrCl 30–49 mL/min) or severe (CrCl 15–29 mL/min) renal impairment, the recommended dose is 15 mg OD.	The recommended dose of apixaban is 2.5 mg taken orally twice daily in patients with NVAF and at least two of the following characteristics: • Age ≥ 80 years • Body weight ≤ 60 kg • Serum creatinine ≥ 1.5 mg/dL (133 µmol/L).	The recommended dose is 30 mg edoxaban once daily in patients with one or more of the following clinical factors: • Moderate or severe renal impairment (creatinine clearance (CrCl) 15 –50 mL/min) • Low body weight ≤ 60 kg • Concomitant use of the following P-glycoprotein (P-gp) inhibitors: ciclosporin, dronedarone, erythromycin, or ketoconazole	Dose reduction recommended: • Patients aged 80 years and over • Patients who receive concomitant verapamil Considerations for dose reduction: • Age 75–80 years • Moderate renal impairment • Gastritis, eosophagitis, GE reflux • Patients at increased risk of bleeding
INR when DOAC can be started	INR≤ 3.0	INR <2	INR≤ 2.5	INR <2
Additional consideration			A trend towards decreasing efficacy with increasing CrCl was observed for edoxaban compared to well-managed warfarin (see section 5.1 for ENGAGE AF-TIMI 48 and additional data from E314 and ETNA-AF). Edoxaban should be used in patients with NVAF and high CrCl only after a careful evaluation of the individual thromboembolic and bleeding risk. Assessment of renal function: CrCl should be monitored at the beginning of the treatment in all patients and afterwards when clinically indicated	Treatment with dabigatran etexilate in patients with severe renal impairment (CrCL <30 mL/min) is contraindicated
Cardioversion	Xarelto can be initiated or continued in patients who may require cardioversion.	Apixaban can be initiated or continued in NVAF patients who may require cardioversion.	Edoxaban can be initiated or continued in patients who may require cardioversion.	Patients can stay on dabigatran
Additional drug interactions	NA	NA	NA	Verapamil dose adjustment is required
Reversal agent	Andexanet alfa	Andexanet alfa	No specific anticoagulant reversal agent	Idarucizumab

BID, twice daily; CrCl, creatinine clearance; DOAC, direct-acting oral anticoagulant; GE, gastroesophageal; INR, international normalised ratio; NA, not available; NVAF, non-valvular atrial fibrillation; NYHA, New York Heart Association; OD, once daily; TIA, transient ischaemic attack.

1. Apixaban SmPC; 2. Dabigatran SmPC; 3. Edoxaban SmPC; 4. Rivaroxaban SmPC.

Appendix 5: EHRA Practical guide on the use of DOACs in NVAF. Effect of drug–drug interactions and clinical factors on DOAC plasma levels and anticoagulant effects

	Via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)
Antiarrhythmic drugs					
Amiodarone	Moderate P-gp inhibition	+12% to 60%	No PK data	+40%	Minor effecta
Digoxin	P-gp competition	No effect	No effect	No effect	No effect
Diltiazem	Weak P-gp and CYP3A4 inhibition	No effect	+40%	No data yet *	No effect
Dronedarone	P-gp and CYP3A4 inhibition	+70% to 100%	With caution	+85% (dose reduction to 30 mg once daily by label)	Moderate effect; should be avoided
Quinidine	P-gp inhibition	+53%	No data yet *	+77% (no dose reduction required by label)	Extent of increase unknown *
Verapamil	P-gp inhibition and weak CYP3A4 inhibition	+12% to 180% (if taken simultaneously) (110 mg BID by label)	No PK data *	+53% (SR) (no dose reduction required by label)	+40% (probably not relevant)
Other cardiovascular drugs					
Atorvastatin	P-gp inhibition and CYP3A4 competition	No relevant interaction	No data yet *	No effect	No effect
Ticagrelor	P-gp inhibition	+24% to 65% (give loading dose 2h after dabigatran)[d]	No data – carefully monitor *	No data – carefully monitor *	No data – carefully monitor *
Antibiotics					
Clarithromycin; Erythromycin	P-gp inhibition and strong CYP3A4 inhibition	Clarithromycin + 19% AUC; + 15% C_{max}	Clarithromycin + 60% AUC; + 30% C_{max}	Erythromycin + 85% AUC; +68% C_{max} (dose reduction to 30 mg once daily by label)	Clarithromycin + 50% AUC; +40% C_{max} Erythromycin + 30% AUC; +30% C_{max}
Rifampicin	P-gp/ BCRP and CYP3A4 induction	-66% AUC; -67% C_{max}	-54% AUC; -42% C_{max}	-35% AUC (but with compensatory increase of active metabolites)	-50% AUC; -22% C_{max}
Antiviral drugs					
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP inhibition or induction; CYP3A4 inhibition	Variable increase/ decrease	Strong increase *	No data yet *	+153% AUC; +55% C_{max} (Ritonavir 600 BID)
Fungostatics					
Fluconazole	Moderate CYP3A4 inhibition	No data yet *	No data yet *	No data yet *	+42% AUC; +30% C_{max} (if given systemically)
Itraconazole; Ketoconazole	Potent P-gp and BCRP competition; strong CYP3A4 inhibition	+140 to 150% (ketoconazole) (US: 2 x 75 mg if CrCl 30–50 mL/min)	+100% AUC; +64% C_{max} (ketoconazole)	+87% AUC; +89% C_{max} (dose reduction to 30 mg once daily by label) (ketoconazole)	+160% AUC; +72% C_{max} (ketoconazole)
Voriconazole	Strong CYP3A4 inhibition	No data yet *	SmPC *	No data yet *	SmPC *
Posaconazole	Mild to moderate P-gp inhibition, strong CYP3A4 inhibition	SmPC *	SmPC *	*	SmPC *

Appendix 5: EHRA Practical guide on the use of DOACs in NVAF. Effect of drug–drug interactions and clinical factors on DOAC plasma levels and anticoagulant effects

	Via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Other drugs					
Naproxen	P-gp competition; pharmacodynamically (increased bleeding time)	No data yet *	+55% AUC; +61% C_{max}	No difference in AUC	No relevant increase of AUC
H2-blockers; PPI; Al-Mg-hydroxide	GI absorption	Minor effect, not clinically relevant	No effect	Minor effect, not clinically relevant	No effect
SSRIs; SNRIs	Pharmacodynamic effect on platelets	SmPC	SmPC *	SmPC *	SmPC
St. John's wort	P-gp/ BCRP and CYP3A4 induction				
Other factors					
Age ≥ 80 years	Potential for increased plasma levels	110 mg BID	[b]	[c]	
Age ≥ 75 years	Potential for increased plasma levels			[c]	
Weight ≤ 60 kg	Potential for increased plasma levels		[b]	(dose reduction to 30mg according to label) [b]	
Weight ≥ 120 kg	Potential for increased plasma levels				
Chronic kidney disease	Potential for increased plasma levels				
Other factors with potentially increased bleeding risk		For example: • Concomitant antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants • Severe Frailty / falls risk • History of bleeding or predisposition (anaemia, thrombocytopenia)			

Adapted from Steffel J et al. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. Europace 2021; 23: 1612–76.

Please refer to Steffel et al. 2021 for full information regarding drug–drug interactions.

Colour coding is based on the respective DOAC SmPC, drug interaction databases, or expert opinion. *indicates no clinical or PK data available. Some of the colour codes will likely require adaptation as more data become available over time.

White: No relevant drug–drug interaction anticipated.

Yellow: Caution required, especially in case of polypharmacy or in the presence of ≥2 yellow/bleeding risk factors.

Orange: Lower dose (dabigatran) or dose reduction (edoxaban) recommended according to label. Red: Contraindicated/not advisable due to increased plasma levels.

Blue (dark): Contraindicated due to reduced NOAC plasma levels.

Blue (light): Caution required, especially in case of polypharmacy or in the presence of ≥2 light blue interactions due to reduced DOAC plasma levels.

AUC, area under the curve; BCRP, breast cancer resistance protein; BID, twice daily; CrCl, creatinine clearance; DOAC, direct-acting oral anticoagulant; NSAID, non-steroidal anti-inflammatory drug; PK, pharmacokinetic; PPI, proton pump inhibitor.

[a]Based on in vitro investigations, comparing the IC50 for P-gp inhibition to maximal plasma levels at therapeutic dose, and/or on interaction analysis of efficacy and safety endpoints in the Phase-3 clinical trials. No direct PK interaction data available.

[b]Dose reduction based on published criteria.

[c]Age had no significant effect after adjusting for weight and renal function.

[d]Data from Phase I study. Interpret in the light of data from Re-DUAL PCI.

Xarelto® (rivaroxaban) 2.5, 10, 15 and 20 mg film-coated tablets & 1mg/ml granules for oral suspension
Prescribing Information
(Refer to full Summary of Product Characteristics (SmPC) before prescribing)

Presentation: 2.5mg/10mg/15mg/20mg rivaroxaban tablet & 1mg/ml granules for oral suspension. **Indication(s):** *2.5mg* Xarelto, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers. Xarelto, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events. *10mg* Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. Treatment of deep vein thrombosis (DVT) & pulmonary embolism (PE), & prevention of recurrent DVT & PE in adults (see W&P for haemodynamically unstable PE patients). *15mg/20mg* Prevention of stroke & systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors such as congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, prior stroke or transient ischaemic attack (SPAF). Treatment of DVT & PE, & prevention of recurrent DVT & PE in adults (see W&P for haemodynamically unstable PE patients). *Paediatrics: 1mg/ml* – Treatment of VTE and prevention of VTE recurrence in term neonates, infants & toddlers, children, & adolescents aged less than 18 years after at least 5 days of initial parenteral anticoagulation treatment. Treatment of VTE & prevention of VTE recurrence in children & adolescents aged less than 18 years & weighing from 30 kg to 50 kg (for 15 mg) / above 50 kg (for 20 mg) after at least 5 days of initial parenteral anticoagulation treatment. **Posology & method of administration:** *2.5mg* – Oral *b.i.d.* dose; patients should also take a daily dose of 75 – 100 mg ASA or a daily dose of 75 – 100 mg ASA in addition to either a daily dose of 75 mg clopidogrel or a standard daily dose of ticlopidine. Start Xarelto as soon as possible after stabilisation, including revascularisation for ACS, and should not be started until haemostasis is achieved in successful lower limb revascularisation for symptomatic PAD; at the earliest 24 hours after admission & at discontinuation of parenteral anticoagulation. If dose is missed take next dose, do not double the dose. *10mg – hip or knee replacement surgery:* Oral *o.d.* dose; initial dose taken 6 to 10 hours after surgery provided haemostasis established. *DVT & PE:* When extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months therapy for DVT or PE), the recommended dose is 10 mg *o.d.*. In patients in whom the risk of recurrent DVT or PE is considered high, such as those with complicated comorbidities, or who have developed recurrent DVT or PE on extended prevention with Xarelto 10 mg *o.d.*, a dose of Xarelto 20 mg *o.d.* should be considered. *15mg/20mg* – Take with food *SPAF:* 20 mg orally *o.d. DVT & PE:* Adults – 15 mg *b.i.d.* for 3 weeks followed by 20 mg *o.d.* for continued treatment & prevention of recurrent DVT & PE; Children & adolescents – calculate dose based on body weight: body weight <30kg refer to the SmPC for Xarelto 1mg/ml granules for oral suspension; body weight 30-50kg take 15mg *o.d.*; body weight >50kg take 20mg *o.d.*. Monitor child's weight & review regularly. Xarelto is not recommended for use in children below 18 years of age in indications other than the treatment of VTE and prevention of VTE recurrence. *All strengths* – Refer to SmPC for full information on duration of therapy & converting to/from Vitamin K antagonists (VKA) or parenteral anticoagulants. ***Special populations:*** Patients undergoing cardioversion: Xarelto can be initiated or continued in patients who may require cardioversion. Patients with non-valvular atrial fibrillation who undergo PCI (percutaneous coronary intervention) with stent placement: There is limited experience of a reduced dose of 15 mg Xarelto once daily (or 10 mg Xarelto once daily for patients with moderate renal impairment [creatinine clearance 30 – 49 ml/min]) in addition to a P2Y12 inhibitor for a maximum of 12 months in patients with non-valvular atrial fibrillation who require oral anticoagulation & undergo PCI with stent placement. ***Renal impairment:*** mild (creatinine clearance 50-80 ml/min) – no dose adjustment; *2.5mg /10mg* – moderate (creatinine clearance 30-49 ml/min) – no dose adjustment. *15mg/20mg* – adults with moderate (creatinine clearance 30-49 ml/min) & severe (creatinine clearance 15-29ml/min) – *SPAF:* reduce dose to 15mg *o.d., DVT & PE:* 15 mg *b.i.d*. for 3 weeks, thereafter 20mg *o.d.* Consider reduction from 20mg to 15mg *o.d.* if patient's bleeding risk outweighs risk for recurrent DVT & PE; children & adolescents with moderate or severe renal impairment (glomerular filtration rate <50 mL/min/1.73 m^2) – not recommended; *All strengths* – Severe impairment: limited data indicate rivaroxaban concentrations are significantly increased, use with caution. Creatinine clearance <15 ml/min – not recommended. ***Hepatic impairment:*** Do not use in patients with coagulopathy & clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C ***Paediatrics:*** Only for treatment of VTE & prevention of VTE recurrence. **Contra-indications:** Hypersensitivity to active substance or any excipient; active clinically significant bleeding; lesion or condition considered to confer a significant risk for major bleeding (refer to SmPC); concomitant treatment with any other anticoagulants except under specific circumstances of switching anticoagulant therapy or when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter; hepatic disease associated with coagulopathy & clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C; pregnancy & breast feeding. Presence of malignant neoplasms at high risk of bleeding. *2.5mg* – concomitant treatment of ACS with antiplatelet therapy in patients with a prior stroke or transient ischaemic attack; concomitant treatment of CAD/PAD with ASA in patients with previous haemorrhagic or lacunar stroke, or any stroke within a month. **Warnings & precautions (W&P):** Clinical surveillance in line with anticoagulant practice is recommended throughout the treatment period. Discontinue if severe haemorrhage occurs. Increasing age may increase haemorrhagic risk. Patients with active cancer: the individual benefit of antithrombotic treatment should be weighed against the risk for bleeding. Gastrointestinal or genitourinary tract tumours have been associated with an increased risk of bleeding. Patients with CAD/PAD: after recent revascularisation procedure of the lower limb due to symptomatic PAD, if required, a dual antiplatelet therapy with clopidogrel, should be short-term, long-term dual antiplatelet therapy should be avoided. Xarelto in combination with other antiplatelets is not recommended. Xarelto should be discontinued at the first appearance of a severe skin rash, or any other sign of hypersensitivity in conjunction with mucosal lesions. 1mg/ml oral suspension - sodium benzoate may increase jaundice in newborn infants (up to 4 weeks old). *Not recommended:* in patients with an increased bleeding risk (refer to SmPC); in patients receiving concomitant systemic treatment with strong concurrent CYP3A4- & P-gp-inhibitors, i.e. azole-antimycotics or HIV protease inhibitors; in patients with prosthetic heart valves; for patients with a history of thrombosis diagnosed with antiphospholipid syndrome; Xarelto should not be used for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR); *2.5mg* treatment in combination with antiplatelet agents other than ASA & clopidogrel/ticlopidine, patients after recent lower limb revascularisation procedures due to symptomatic PAD with a previous stroke or TIA receiving dual antiplatelet therapy; *10mg/15mg/20mg* in haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy; *1mg/1ml* in children less than 6 months of age who at birth had <37 weeks of gestation, a body weight of <2.6 kg, or had <10 days of oral feeding; in children ≥1 year old with moderate or severe renal impairment (glomerular filtration rate <50 mL/min/1.73 m^2); in children ≤1 year old with serum creatinine results >97.5th percentile. *Use with caution:* in patients treated concomitantly with medicines affecting haemostasis; when neuraxial anaesthesia or spinal/epidural puncture is employed; in patients at risk of ulcerative gastrointestinal disease (prophylactic treatment may be considered); *2.5mg* in patients ≥75 years of age or with lower body weight (<60kg); in CAD patients with severe symptomatic heart failure. Patients on treatment with Xarelto & ASA or Xarelto & ASA plus clopidogrel/ticlopidine should only receive concomitant treatment with NSAIDs if the benefit outweighs the bleeding risk. *2.5mg/10mg* in patients with moderate renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations; *15mg/20mg* in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations; *1mg/ml* in children with cerebral vein & sinus thrombosis who have a CNS infection. *All strengths* – There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests. Xarelto tablets contains lactose. **Interactions:** Concomitant use with strong inhibitors of both CYP3A4 & P-gp not recommended as clinically relevant increased rivaroxaban plasma concentrations are observed. Avoid co-administration with dronedarone. Use with caution in patients concomitantly receiving NSAIDs, ASA or platelet aggregation inhibitors due to the increased bleeding risk; use with caution in patients concomitantly receiving SSRIs/SNRIs due to a possible increased bleeding risk. Concomitant use of strong CYP3A4 inducers should be avoided unless patient is closely observed for signs & symptoms of thrombosis. **Pregnancy & breast feeding:** Contra-indicated. **Effects on ability to drive & use machines:** syncope (uncommon) & dizziness (common) were reported. Patients experiencing these effects should not drive or use machines. **Undesirable effects:** *Common:* anaemia, dizziness, headache (in children: very common), eye haemorrhage, hypotension, haematoma, epistaxis (in children: very common), haemoptysis, gingival bleeding, GI tract haemorrhage, GI & abdominal pains, dyspepsia, nausea, constipation, diarrhoea, vomiting (in children: very common), increase in transaminases, pruritus, rash, ecchymosis, cutaneous & subcutaneous haemorrhage, pain in extremity, urogenital tract haemorrhage (menorrhagia *very common* in women <55 yrs treated for DVT, PE & prevention of recurrence, common in female adolescents after menarche), renal impairment, fever (in children: very common), peripheral oedema, decreased general strength & energy, post-procedural haemorrhage, contusion, wound secretion. *Serious: cf. CI/Warnings & Precautions – in addition:* thrombocytosis, thrombocytopenia (in children: common), Stevens-Johnson syndrome/Toxic Epidermal Necrolysis, DRESS syndrome, anaphylactic reactions including shock, angioedema & allergic oedema, occult bleeding/haemorrhage from any tissue (e.g. cerebral & intracranial, haemarthrosis, muscle) which may lead to complications (incl. compartment syndrome, renal failure, anticoagulant-related nephropathy or fatal outcome), syncope, tachycardia (in children: common), hepatic impairment, cholestasis & hepatitis (incl. hepatocellular injury), increases in bilirubin (in children: common), blood alkaline phosphatase & GGT, increased conjugated bilirubin, jaundice, vascular pseudoaneurysm following percutaneous vascular intervention, eosinophilic pneumonia. Prescribers should consult SmPC in relation to full side effect information. **Overdose:** In the case of an overdose, the patient should be observed carefully for bleeding complications and other adverse reactions. A specific reversal agent is available, refer to the SmPC for andexanet alfa. **Legal Category:** POM. **Package Quantities & Basic NHS Costs:** *2.5mg* – 56 tablets: £50.40. *10mg* – 10 tablets: £18.00, 30 tablets: £54.00 & 100 tablets: £180.00. *15mg* – 14 tablets: £25.20, 28 tablets: £50.40, 42 tablets: £75.60, 100 tablets: £180.00; *20mg* – 28 tablets: £50.40, 100 tablets £180.00; Treatment Initiation pack (42 tablets of 15mg, 7 tablets of 20mg): £88.20 *1mg/ml* – 100ml bottle: £9.00, 250ml bottle: £18.00 **MA Number(s):** *Great Britain: 2.5mg* – PLGB 00010/0708. *10mg* – PLGB 00010/0705. *15/20mg* – PLGB 00010/0706, 0707, 0709. *1mg/ml* – PLGB 00010/0746. *Northern Ireland: 2.5mg* – EU/1/08/472/025-035, 041, 046-047. *10mg* – EU/1/08/472/001-010, 022, 042-045 *15mg/20mg* – EU/1/08/472/011-016, 017-021, 023-024, 036-040, 048-049. *1mg/ml* – EU/1/08/472/050-051 **Further information available from:** Bayer plc, 400 South Oak Way, Reading, RG2 6AD, U.K. Telephone: 0118 206 3000. **Date of preparation:** July 2023

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Adverse events should be reported.
Reporting forms and information can be found at https://yellowcard.mhra.gov.uk or search for MHRA Yellow Card in Google Play or Apple App Store.
Adverse events should also be reported to Bayer plc.
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Email: pvuk@bayer.com