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How to choose the best NOAC for patients with atrial fibrillation

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Abstract

A non-Vitamin K antagonist oral anticoagulant (NOAC) is an attractive option for many patients with atrial fibrillation (AF). The various NOACs have slightly different properties, and thus prescribing NOACs should be based on patient characteristics. With several NOACs to choose from, this article offers a patient-centred approach in choosing the best choice of NOACs for non-valvular AF patients.

Key words: ANTICOAGULANTS / therapeutic use
ATRIAL FIBRILLATION / drug therapy
VITAMIN K / antagonists & inhibitors
WARFARIN / therapeutic use

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with two-fold increased risk of dying[1] with 5-fold increase in stroke risk[2] representing a major healthcare burden worldwide. Over the past 20 years, hospital admissions for AF have increased by 60%, and it is also estimated that AF prevalence will triple by 2050[3].

The risk of stroke in AF patients is not homogenous and depends on additional stroke risk factors[4,5]. Effective stroke prevention means oral anticoagulation, and the Vitamin-K antagonists (VKAs, e.g. warfarin) and non-VKA oral anticoagulants (NOACs) have been recommended by European Society of Cardiology (ESC) guidelines[6].

All NOACs were studied in large, well-designed randomized trials and had undergone extensive evaluation, with meta-analyses showing reduction of total mortality, cardiovascular mortality, intracranial bleeding and overall bleeding in comparison to warfarin[7,8].

With several NOACs to choose from, this article offers a brief and patient-centred approach in selecting the appropriate NOAC according to individual patient characteristics. This review is crafted into three sections: a) the initial approach in choosing oral anticoagulants (OAC), b) time in therapeutic range (TTR) in warfarin and c) selecting NOACs based on specific populations.

The initial approach

The approach to the use of OAC for stroke is by first identifying the 'truly low risk' patients (CHA_2DS_2-VASc score of 0 [men] or 1 [women])[9-12] who do not need antithrombotic therapy[13]. Those who are eligible for oral anticoagulants (that is, CHA_2DS_2-VASc score of ≥2, or 1 for men), the SAMe-TT_2R_2 score can help identify patients who will do well with VKAs (TTR ≥ 70%). Those patients with SAMe-TT_2R_2 score >2 are less likely to do well with VKAs and would be better off with a NOAC. See Figure 1 flow chart.

VKAs: Does time in therapeutic range (TTR) matter?

Quality of anticoagulation control is crucial in managing AF. Warfarin is used by millions of patients worldwide to prevent strokes or to prevent or treat venous thromboembolism (VTE). Warfarin offers its best efficacy and safety when the average TTR is >65-70% in a particular individual[9]. TTR is an effective way of examining whether patients are achieving the optimum benefit from taking warfarin. A suboptimal TTR (e.g. <60%) is related to more adverse effect, exposing the patient to both adverse bleeding and thromboembolic events[14-16].

The SAMe-TT_2R_2 score (table 1) is a new clinical risk score developed to predict warfarin response in

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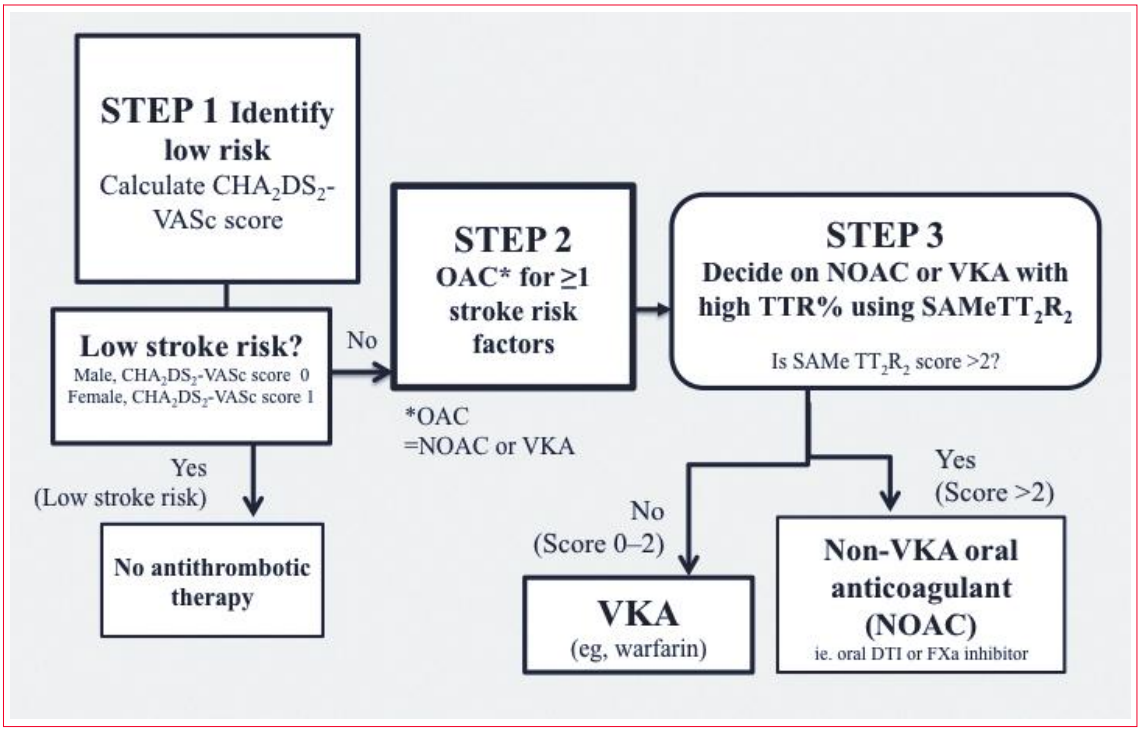

Figure 1. The AF patient manager pathway

AF thus help in decision-making between warfarin or NOACs[17]. National Institute for Health and Care Excellence (NICE) NOAC implementation Collaborative consensus document in the United Kingdom has recommended use of the SAMe-TT2R2 score[18] as well as an ESC Working Group on Thrombosis Anticoagulation Task Force consensus document[6].

Patients with SAMe-TT_2R_2 score 0 to 2 are highly likely to achieve high TTR and thus could be treated with VKAs. Patients with SAMe-TT_2R_2 score of more than 2 are associated with poor TTR. The options for them would be either to select a NOAC or improve education and careful review/follow up regarding anticoagulation control to improve TTR[9]. See table 1 and 2 for the SAMe-TT_2R_2 score.

When well controlled and well managed, warfarin is an effective means of stroke prevention. Due to its recognized limitations, a large proportion of patients who are at high risk of stroke remained under-treated[19]. Although patients who are well controlled and well managed on warfarin ought not to be immediately transitioned to a NOAC, the latter drugs have been demonstrated to significantly reduce intracranial bleeding and that this clinical benefit persists irrespective of the level of INR control[20].

Warfarin would remain as the first-line oral anticoagulant for patients with mechanical heart valves. Table 3 summarises the conditions where NOACs are unsuitable.

NOACs

The NOACs possess many desirable advantages especially in the context of patient convenience. There is however paucity of evidence to recommend one agent over another as there is no head-to-head data comparing the NOACs. Suggestions provided are based on their pharmacological profiles.

The four currently licensed NOACs can be divided into two groups – (i) direct thrombin inhibitor (e.g. dabigatran), and (ii) Factor Xa inhibitors (e.g. rivaroxaban, apixaban and edoxaban). As all NOACs have slightly different properties, prescribing them should be based on case-by-case characteristics.

Drug-drug interactions and co-prescribing

Although it is expected that drug interactions are considerably fewer with the NOACs[21], there are still relevant interactions. Clinicians must be aware of the pharmacokinetic effects of accompanying drugs, especially permeability-glycoprotein (P-gp) and cytochrome P3A4 (CYP3A4) inhibitors and inducers.

P-gp is one of the drug transporters and its activity is modulated by a variety of drugs, herbs and

Table 1. The SAMe-TT_2R_2 score's acronym and definition.

Acronym	*Definitions*	*Points*
S	Sex (female)	1
A	Age (<60 years)	1
Me	Medical history *	1
T	Treatment (interacting drugs e.g. amiodarone)	1
T	Tobacco use (within 2 years)	2
R	Race (non Caucasian)	2
Maximum points		8

* more than two of the following: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral artery disease, congestive heart failure, previous stroke, pulmonary disease, and hepatic or renal disease. Adapted from (9,17)

Table 2. Predicting warfarin response in patients with atrial fibrillation (9,17)

Score	
0-1	Likely to achieve a high TTR (e.g. >65%) thus a VKA is likely beneficial
>2	Associated with a poor TTR thus less likely to do well on a VKA. Options: Select a NOAC or, Improve TTR by education

TTR: time in therapeutic range, VKA: vitamin-K antagonist

food components[22]. CYP3A4, a member of the hepatic cytochrome P450, is expressed in adult human liver and is responsible for the oxidative metabolism of a wide variety of drugs[23]. In general, P-gp and CYP3A4 inducers reduce the bioavailability and plasma levels of its substrate, while P-gp and CYP3A4 inhibitors increase the bioavailability and plasma levels of its substrate.

All NOACs are substrates of P-gp and their absorption is dependent on the intestinal P-glycoprotein (P-gp) system[24]. Factor Xa inhibitors are affected by both P-gp and CYP3A4 inhibitors and inducers[25-27]. However, edoxaban undergoes CYP3A4 metabolism to a lesser degree (<5%) than rivaroxaban and apixaban[28]. Dabigatran has no significant involvement of the CYP3A4 pathway[29].

Strong inhibitors of CYP3A4 and P-gp, for example, azole antifungals, should not be co-administered with the NOACs as this increase NOACs area under the curve (AUC) with parallel increase in maximum concentration[27,30-33] placing patients at increased risk of bleeding. Concurrent therapy of strong CYP3A4 and P-gp inducers should also be avoided or used with caution. The exception is perhaps edoxaban, while for apixaban this interaction may lead to reduced plasma concentrations[26].

For dabigatran, P-gp inhibitors and renal impairment can further increase dabigatran plasma concentrations. A reduced dose of dabigatran (75 mg twice daily) is recommended when combined with strong P-gp inhibitors in patients with CrCl 30-50 mL/min. For patients with CrCl <30 mL/min, dabigatran is not recommended if a P-gp inhibitor is co-administered[30,34]. Co-administration with strong P-gp inducers should also be avoided as dabigatran concentration is reduced, placing patients at risk of thrombosis[30,32,34].

In summary, for practical purposes, verapamil, amiodarone and dronedarone are the most important drugs that can increase the concentrations of all NOACs, and some extra caution is advised for patients with renal impairment. Concurrent therapy of moderate to strong CYP3A4 and P-gp inducers and inhibitors will require either dose adjustment or discontinuation of the NOACs[25-27,30]. Patients should be monitored for bleeding or loss of anticoagulant effect in this situation.

Table 4 showed examples of potent P-gp and CYP3A4 inhibitors/inducers.

Renal impairment. Patients with chronic kidney disease (CKD) and atrial fibrillation are at risk for both thromboembolic events and bleeding[35,36]. A creatinine clearance (CrCl) of <50-60 mL/min is

Table 3. Conditions where NOACs are unsuitable.

Prosthetic heart valves
Severe renal impairment
Severe hepatic impairment with associated coagulopathy
Compliance issue where monitoring is essential
High-risk for bleeding (as there is lack of antidote)
Significant underweight (<50kg) or significant obesity (>120kg)
Pregnancy and breast-feeding

an independent risk factor of stroke and systemic embolism[37,38]. The four NOACs have different renal elimination characteristics: dabigatran has the highest renal clearance (up to 80%)[39,40], while edoxaban, rivaroxaban and apixaban have renal clearance of 50%[29], 36%[41] and 27%[42] respectively. Thus NOACs should be used with caution in patients with renal impairment.

In the United Kingdom, the estimated glomerular filtration rate (eGFR) is the standard method used to determine renal function, but it was not design for drug dosing decisions. The European Heart Rhythm Association (EHRA) of the European Society of Cardiology (ESC) practical guide on the NOACs has suggested using creatinine clearance, the Cockcroft & Gault equation, as all trials with NOACs used this measure for estimating kidney function for drug use and dosing decisions[6].

There is lack of efficacy and safety data in patients with severe renal dysfunction as they were excluded from all NOACs large clinical trials. RELY (dabigatran) and ROCKET AF (rivaroxaban) excluded patients with creatinine clearance (CrCl) of <30 mL/min while ARISTOTLE (apixaban) excluded patients with a CrCl of <25 mL/min (or a creatinine of >2.5 mg/dL). However, patients with mild-to-moderate CKD were enrolled, with or without pre-specified dose reductions.

Dabigatran doses used in RELY were 150 mg and 110 mg twice daily with no dose adjustment based on CrCl[43]. The FDA however has approved a dose of 75 mg twice daily, based on pharmacokinetic modelling, for patients with CrCl of 15-30 mL/min[44,45]. In severe renal impairment, dabigatran's plasma half-life increased at least two-fold[40] thus exaggerating anticoagulant effect.

In ROCKET AF, a reduced dose of 15 mg (from 20 mg) once daily was used in patients with CrCl of 30-50 mL/min. It showed non-inferiority to warfarin for the primary safety endpoint thus presenting a reasonable alternative to VKA in those patients [46]. Rivaroxaban is contraindicated in patients with CrCl <15 mL/min[27].

In ARISTOTLE, a reduced dose of 2.5 mg (from 5 mg) twice daily was used in patients with CrCl of <25 mL/min plus one of the following criteria: age more than 80, body weight less than 60 kg or elevated serum creatinine >1.5 mg/dL[47]. A subgroup analysis comparing patients with normal renal function, mild renal function and moderate renal dysfunction showed that the hazard ratios for stroke, systemic embolism and all-cause mortality favoured apixaban over warfarin[36].

The Hokusai-VTE (for venous thromboembolism) and ENGAGE AF-TIMI 48 (for AF) studies mandated dose reduction for patients with renal impairment[48,49]. A reduced dose of 30 mg (from 60 mg) edoxaban is mandated for: 1) CrCl 15-50 mL/min, 2) weight less than 60 kg and, 3) used of strong P-glycoprotein (P-gp) inhibitors[26]. Edoxaban should also not be used in the normal range of CrCl >95 mL/min as it will lead to reduced efficacy[26] and increased ischaemic stroke compared with warfarin.

In summary, the use of NOACs in patients with severe renal impairment is discouraged [6] (see table 5). In mild to moderate renal impairment, NOACs are at least as effective as well-controlled warfarin and at least as safe (dabigatran, rivaroxaban) or safer (apixaban) in terms of haemorrhage risk [46,50]. Renal function should also be monitored yearly in cases of mild impairment, twice a year in moderate impairment and more frequently in situations that can worsen renal function [6] e.g. hypovolemia, dehydration, and certain co-medication.

Hepatic impairment. Impaired hepatic function can affect coagulation and these patients are at increased risk of bleeding. The recommended, and most widely used, categorization to describe chronic liver impairment is the Child-Pugh classification: A, B and C or mild, moderate and severe[13,51,52]. There are limited data regarding the use of NOACs with hepatic impairment.

The RE-LY, ROCKET AF, and ARISTOTLE trials excluded patients with significant hepatic impairment (based on their baseline ALT[43,47,53], AST[43,53], ALP[43] or total bilirubin[53] as well as patients with active liver disease [e.g. acute hepatitis, chronic active hepatitis, and cirrhosis][43,47,53]. The monitoring of liver function throughout these studies, however, did not show any toxicity[43,54,55]. Regulatory guidance and label restrictions however have been produced to identify patients at risk and whether dose adjustment or contraindication is required.

Table 4. Strong P-gp/CYP3A4 drugs and the NOACs

	Dabigatran	*Rivaroxaban*	*Apixaban*
P-gp inducers (increase risk of stroke/VTE)			
1. Rifampicin	Avoid	Avoid	Avoid
P-gp inhibitors(increase bleeding risk)			
1. Ketoconazole 2. Amiodarone 3. Verapamil 4. Quinidine	Reduce to 75mg bd	Avoid	Reduce apixaban dose by half; or avoid in those already on the reduced dose.
CYP3A4 inducers (increase risk of stroke/VTE)			
1. Rifampicin 2. Carbamezipine	No effect on CYP3A4	Avoid	Avoid
CYP3A4 inhibitors (increase risk of bleeding)			
1. Ketoconazole 2. Clarithromycin 3. Protease inhibitors	No effect on CYP3A4	Avoid	Reduce apixaban dose by half; or avoid in those already on the reduced dose.

bd, twice daily; CYP3A4, cytochrome P450; P-gp,permeability glycoprotein; od, once daily. Consult Summary of Product Characteristics (SPC) for full details of interactions.

Table 5. NOACs dosage modifications in NVAF patients with renal impairment

	Renal clearance	*CrCl >50 mL/min*	*CrCl 30-49 mL/min*	*CrCl <29 mL/min*	*Additional information*
Dabigatran	>80%	150 mg bd	110 mg bd	Avoid	
Rivaroxaban	33%	20 mg od	15 mg od	Avoid	
Apixaban	25%	5 mg bd	2.5 mg bd	Avoid	
Edoxaban	50%	60 mg od	30 mg od	Avoid if CrCl <15 mL/min	Avoid if CrCl >95 mL/min

bd, twice daily; od, once daily; CrCl, creatinine clearance.

Dabigatran is not metabolised in the liver. Moderate hepatic impairment was not shown to affect the pharmacodynamic or pharmacokinetic of dabigatran and thus dabigatran can be given without dose adjustment in this group[56]. Dabigatran is contraindicated in Child-Pugh's C, elevated liver enzymes >2x upper limit of normal (ULN), as well as hepatic impairment expected to affect survival[30,57].

Factor Xa inhibitors are metabolized by the liver (CYP3A4 involvement). Child-Pugh B's patients taking rivaroxaban did experience >2-fold increase in exposure and thus is contraindicated in Child-Pugh's B or C[58], including liver disease associated with coagulopathy and clinically relevant bleeding risk[27]. In moderate liver impairment, the AUC for plasma concentration time is increased by 1.09-fold for apixaban (compared to rivaroxaban 2.27-fold). Apixaban can thus be given, with caution, to patients with mild and moderate hepatic impairment or ALT and AST levels >2x ULN[57]. In Japan, edoxaban has not been restricted for use in liver impairment, however advises care in patients with severe liver impairment[57].

In summary, it is prudent to screen liver enzymes, bilirubin and the coagulation status (aPTT, PT) before prescribing any long-term anticoagulant. Monitoring them should also be performed on regular basis. The four NOACs can be used in mild liver impairment (Child-Pugh A), but none should be given in severe hepatic impairment (Child-Pugh C). Dabigatran and apixaban can be given in patients with moderate liver impairment (Child-Pugh B) provided there is no

Table 6. NOACs and recommendations in hepatic impairment

	Dabigatran	*Rivaroxaban*	*Apixaban*	*Edoxaban*
Mild (Child-Pugh A)	No restriction	No restriction	Use with caution	No restriction
Moderate (Child-Pugh B)	No restriction	Avoid	Use with caution	Avoid
Severe (Child-Pugh C)	Avoid	Avoid	Avoid	Avoid

Data pooled from (57,59)

clinically relevant bleeding risk present. Dose reduction is not needed for any of the NOACs: it can be given with severe caution or (preferably) should be avoided, especially since liver impairment can be associated with a coagulopathy [57] (see table 6). VKA with INR guidance, as well as low molecular-weight heparin, can be applied as alternative treatment options especially in patients with hepato-renal syndrome.

Triple therapy (in non valvular AF patients who are on NOACs and undergoing percutaneous coronary intervention) Dual antiplatelet therapy (DAPT), consisting of aspirin and a $P2Y_{12}$ inhibitor, has been proven beneficial in patients with recent myocardial infarction (MI) or percutaneous coronary intervention (PCI) [60-62]. DAPT prevents stent-thrombosis and significantly reduced the rate of MI, stroke and mortality [60-62]. However it is also associated with an increased risk of bleeding compared to single antiplatelet therapy (SAPT) [60].

Approximately 34% of non-valvular AF patients have co-existing ischaemic heart disease [63]. Triple therapy (TT, ie. antithrombotic + DAPT) is often indicated in these patients in the setting of acute coronary syndromes (ACS), however should always be considered to carry an increased risk of overall bleeding [28,64], as also reported in the WOEST trial (for VKAs) and the nationwide registry data from Denmark [65]. Triple therapy is thus complex and challenging when it comes to balancing the risks of thromboembolism, serious bleeding, stent thrombosis, and major adverse or recurrent cardiac events [66].

Only a few studies have examined the use of NOACs in TT in patients with ACS[67-69]. These studies are difficult to compare because of the different definitions used (particularly regarding bleeding), and the many variables involved (procedural variables, difference in age, severity of comorbidity and stable/unstable patients).

Real-world data has shown that dabigatran 110 mg twice daily, when compared with warfarin), is associated with decreased incidence of gastrointestinal bleeding but increased with dabigatran 150 mg twice daily[70,71]. However, dabigatran both 150 mg and 110 mg twice daily, has been associated with an increased incidence of MI compared to warfarin [43,72,73] although this may be attributed to the cardio protective action of warfarin[74]. Low-dose rivaroxaban 2.5 mg twice daily (combined with standard antiplatelet therapy) showed a positive benefit-risk profile with a significant reduction in the composite efficacy endpoint of cardiovascular death, myocardial infarction (MI) and stroke compared with placebo[67] although the rate of major bleeding was significantly increased. Moreover, there is also significant reduction in cardiovascular mortality and all-cause mortality[74].

A joint consensus document from the European Society of Cardiology (ESC) Working Group of Thrombosis, the European Heart Rhythm Association (EHRA), the European Association of Acute Cardiac Care (ACCA), and the European Association of Percutaneous Cardiovascular Interventions (EAPCI), has provided specific recommendations on the duration of combined antithrombotic and SAPT or DAPT, dependent on an individual patient risk profile: stroke risk, bleeding risk, and the clinical setting (elective percutaneous coronary intervention or urgent percutaneous coronary intervention)[66].

Non-valvular AF (NVAF) patients in the setting of ACS events are recommended to continue an existing OAC. Likewise, an OAC (VKA or NOACs) should be started in ACS patients who develop new-onset AF while on DAPT. Depending on HAS-BLED and CHA_2DS_2-VASc scores of individuals, the current strategies include: 1) low doses of aspirin (75-100 mg/day), 2) clopidogrel 75 mg/day is used (instead of the newer and more potent $P2Y_{12}$ inhibitors ticagrelor or prasugrel), 3) the less thrombogenic newer generation drug-eluting stent (DES) preferred to bare metal stent (BMS) or first generation DES, 4) the duration of TT should be as

minimized as possible, and 5) if NOACs are used, the lower tested dose for stroke prevention in NVAF should be considered (rivaroxaban 15 mg once daily, apixaban 2.5 mg twice daily or dabigatran 110 mg twice daily). The duration of combined therapy is not covered in this article however we also offer the reader to the website for comprehensive information [75] (DOI:10.1093/eurheartj/ ehv320).

Currently there are on going trials; for example, PIONEER AF-PCI (clinical trial identifier NCT01830543) and REDUAL-PCI (clinical trial identifier NCT02164864); exploring NOACs in NVAF patients undergoing PCI.

Dyspepsia-symptoms. In the RE-LY trial, dyspepsia-like symptoms were the only adverse effects that were significantly increased in dabigatran-treated patients compared to controls. It was reported twice as many in subjects receiving dabigatran (DE 110 mg 11.8%, 150 mg 11.3% total rate; dose independent) compared to those receiving warfarin (5.8% total rate)[43]. Dyspepsia-like symptoms in the RE-LY trial include upper abdominal pain, abdominal discomfort, epigastric discomfort and dyspepsia[43]. The dyspepsia-like symptoms were generally mild or moderate, with dabigatran 110 mg having the highest frequency[43]. These have led to non-adherence and discontinuation of dabigatran.

From the data of the long-term follow-up study RELY-ABLE, Nieuwlaat et al reported that dyspepsia-like symptoms can be transient; with symptom improvement following concomitant food intake, H2-blockers or proton pump inhibitors (PPI)[76]. The absorption of dabigatran etexilate is however dependent on an acidic milieu in the gastrointestinal tract[77]. The EHRA guidelines comment that co-administration of PPI and H2-blockers causes a small reduction on the bioavailability of dabigatran[78]. However this does not affect the clinical efficacy of dabigatran, with no dose adjustment needed, thus antacid intake is not contraindicated[28,78].

A survey conducted by Choi et al found that patients using dabigatran were significantly more likely to experience gastrointestinal symptoms (indigestion, regurgitation, nausea and stomach pain) compared to patients using warfarin. However, the dabigatran users used additional medications to treat these symptoms and that they were willing to tolerate the side effects based on perceptions of high efficacy and convenience[79].

A recent Danish nationwide cohort study found that in patients with NVAF with no history of gastrointestinal diseases, initiation of dabigatran was not associated with an increased risk of upper dyspepsia-like diagnoses, gastrointestinal bleeding requiring hospitalization, subsequent PPI use or gastroscopy compared with warfarin[80]. However, anticoagulation-naive patients dosed with dabigatran 110 mg twice daily were more often prescribed PPI subsequently compared to warfarin-treated patients. The authors felt that "this might indicate selection bias towards that patients more prone to gastrointestinal adverse effects were started on lower dose dabigatran to avoid symptoms, with addition of a high mean age (80.0, SD 8.7), CHA_2DS_2-VASc score (3.6, SD 1.4), and a HAS-BLED score (2.3, SD 1.0) indicating a poorer condition than the other groups" [80].

Dyspepsia is uncommon with rivaroxaban, apixaban or edoxaban [43,47,53]. As dabigatran is taken with food to reduce the risk of dyspepsia[81], rivaroxaban is taken with food to enhance absorption and bioavailability[82].

In summary, dyspepsia can occur in dabigatran users but is usually self-limited, mild in intensity and the use of acid suppressive therapies does not affect the NOAC efficacy.

The Elderly (aged ≥75 years) AF is a significant problem of the elderly with 23.5% of strokes in individuals aged ≥ 80 were attributable to AF [2]. It affects <2% of the population younger than 65 years, approaching up to 10% in patients older than 80 years [83]. Age ≥75 itself is considered a risk factor in stroke risk-stratification schemes and contributes 2 points towards a maximum risk score of 9 in the cardiac failure, hypertension, age, diabetes mellitus, stroke/TIA/VTE, vascular disease and gender (CHA_2DS_2-VASc) scheme[84,85].

However, the ATRIA cohort found that OAC in this age group is still underutilized (35% in the > 85 years old compared to 62% in the < 74 years old)[86]. The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) trial was a major step forward in firmly establishing that the population of elderly benefit as much as younger patients from warfarin treatment. Even among elderly patients with AF, anticoagulation with adjusted-dose warfarin was superior to aspirin for primary stroke prevention with significant reductions in the rates of overall stroke, disabling non-fatal stroke and ischaemic stroke. The study also provides welcome reassurance about the efficacy and safety of warfarin with no increased bleeding risk with age[87].

Despite this evidence, the fear of bleeding has often led the elderly being denied OAC[88]. The elderly have high prevalence of multiple comorbidities (such as renal impairment), low body mass index, poly pharmacy (such as taking both aspirin and clopidogrel for cardiac stent patency), falls,

Table 7. Dose adjustments for NOACs.

Dabigatran 110 mg BD (Instead of 150 mg BD) NB. 75 mg capsules are not licensed for AF	*Rivaroxaban 15 mg OD (Instead of 20 mg OD) NB. 10 mg tablets are not licensed for AF*	*Apixaban 2.5 mg OD (Instead of 5 mg OD)*	*Edoxaban*
• Age > 80 years old	• CrCl 30-49 mL/min	• Concomitant use of interacting drugs	Avoid in CrCl > 95 mL/min
• CrCl 30-50 mL/min	• HAS-BLED ≥ 3	If ≥ 2 of:	
• Concomitant use of interacting drugs		• Age ≥ 80 years	
• HAS-BLED ≥ 3		• Body weight ≤ 60 kg	
		• Creatinine ≥133 μmol/L	

CrCL, creatinine clearance; bd, twice daily; od, once daily; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly

haemorrhage, cognitive impairment and poor treatment adherence[89].

The RE-LY, ROCKET-AF, ARISTOTLE and ENGAGE AF-TIMI 48 trials had well represented NVAF patients over 70 years of age. A recent meta-analysis of these trials evaluating the efficacy and safety of NOACs in this subgroup demonstrated of non-inferiority when compared to dose-adjusted warfarin[90] in preventing stroke and systemic embolic events. In patients aged ≥ 75 years compared with those aged < 75 years, each of the NOACs did not lead to greater major or clinically relevant bleeding than warfarin[90], and significantly reduced the risk of stroke and systemic embolism. In the RE-LY study, dabigatran 150 mg demonstrated higher rates of major bleeding particularly extra cranial haemorrhage compared to warfarin[91] in patients ≥ 75 years, hence the recommendation to use the 110 mg dose in the elderly.

Corsonello et al. found that [92] multiple daily dosing in the elderly is associated with lower medication adherence, compared to overall number of drugs and age. In this case, rivaroxaban is an attractive option as it is a once daily drug. However, *Vrijens et al*. found that although once-daily dosing increase absolute adherence, twice-daily dosing regimens are more forgiving in patients with suboptimal adherence[93]. The ability to swallow medicines is also important; only rivaroxaban and apixaban can be crushed and given via gastric tube. For patients who require medication in a compliance aid, rivaroxaban and apixaban are the preferred options as no special storage requirement is needed.

In summary, the efficacy and safety of all NOACs are preserved in advanced age, however the decision is best based on their co-morbidities, compliance and personal preferences. The fewer drug-drug interactions and fixed doses without routine coagulation monitoring of NOACs have further simplified OAC for the elderly.

See Table 7 for NOACs dose adjustments. See Figure 2 for algorithm for choosing NOACs.

Conclusion

On the safety and efficacy side, NOACs when used correctly (and appropriately) represent a clear advantage over warfarin in preventing stroke and systemic embolism in NVAF patients. When choosing a NOAC, three questions need to be borne in mind: 1) patient's bleeding risk (HAS-BLED score ≥ 3 is deemed high risk for bleeding), 2) patient characteristics and 3) patient's preference and compliance to NOAC. Prescribers may find it helpful to become familiar with a particular NOAC, but the choice simply need to be individualized to patient clinical characteristics, with some active participation from the patient in this decision-making process.

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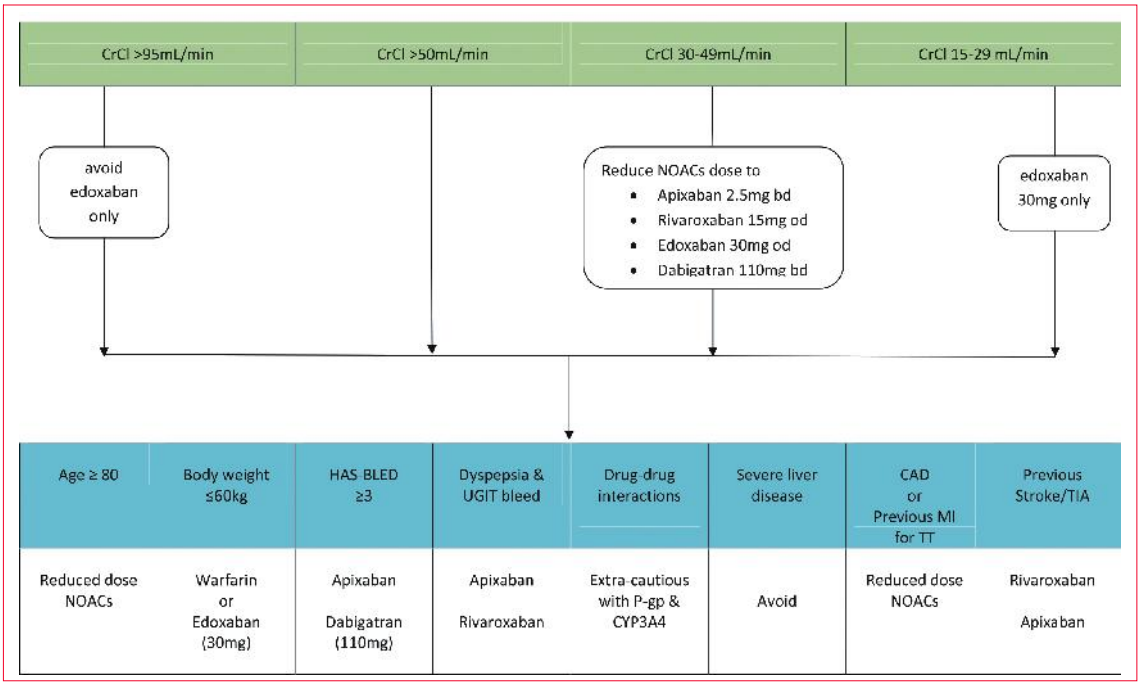

Figure 2. Algorithm for NOACs' candidacy

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