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REVIEW ARTICLE

Non-Vitamin K Antagonist Oral Anticoagulants: New Choices for Patient Management in Atrial Fibrillation

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Abstract Atrial fibrillation (AF) is a significant problem for the aging population and remains a major factor underlying stroke risk. Warfarin anticoagulation has been proven effective for stroke prevention in AF, but can be difficult to manage and requires frequent monitoring. The non-vitamin K antagonist oral anticoagulants (NOACs) have been shown to be as effective as warfarin for stroke prevention in nonvalvular AF (NVAF) and are associated with a reduced risk of bleeding compared with warfarin. Dabigatran, rivaroxaban, apixaban, and edoxaban have been approved in the USA for reducing the risk of stroke in patients with NVAF. In this article, AF risk assessment is discussed and NOAC phase III clinical trials for the prevention of stroke and systemic embolic events are reviewed. Further, differences in stroke and bleeding outcomes between NOACs are highlighted, the use of NOACs for cardioversion and special patient populations is discussed, and management considerations for patients with AF are reviewed.

Key Points

Non-vitamin K oral anticoagulants (NOACs) are as effective as warfarin for stroke prevention in atrial fibrillation and are associated with less intracranial bleeding.

NOACs may provide a simpler, safer alternative to warfarin.

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1 Introduction

As the US population ages and obesity rates increase, the incidence of atrial fibrillation (AF) is projected to reach 2.6 million cases by 2030 [1]. In the 1991 Framingham study, individuals with AF had a five-times-greater risk of stroke, higher than the risk conveyed by coronary heart disease (2×), hypertension (3×), or cardiac failure (4×) compared with asymptomatic individuals [2]. AF is an independent risk factor for stroke [2] that is present in approximately 10 % of patients aged 50–59 years, increasing to 45 % in those aged ≥90 years [3].

Anticoagulation is recommended for patients with AF and prior stroke or transient ischemic attack, or for those who are at moderate risk of stroke based on sex, age, vascular disease, diabetes, congestive heart failure, or hypertension [4]. Among patients with AF deemed at moderate to high risk for stroke, anticoagulation is a cost-effective treatment for stroke prevention, and may potentially reduce the substantial financial burden associated with stroke due to healthcare costs [5, 6]; nevertheless, it remains underused [7]. Reasons for this underuse typically include concerns over increased risk of bleeding as well as limitations in healthcare access, facility availability, physician awareness, the inconvenience of monitoring international normalized ratio (INR) levels, and patient compliance [8, 9].

Non-vitamin K antagonist (VKA) oral anticoagulants (NOACs) are at least as effective as warfarin for the prevention of stroke in AF and are associated with significantly decreased risks of intracranial hemorrhage [10]. Dabigatran, rivaroxaban, apixaban, and edoxaban have been approved for reducing the risk of stroke in patients with nonvalvular AF (NVAF) [11–14]. Current guidelines,

published prior to the approval of edoxaban, recommend dabigatran, rivaroxaban, apixaban, and warfarin for use in NVAF, and further recommend NOACs for patients who are unable to maintain a therapeutic INR on warfarin [4, 15]. Reasons for an inability to maintain a stable INR include patient non-compliance with dietary restrictions, missed doses, and failure to routinely monitor and thus adjust doses when needed, drug–drug interactions, and genetic variability that can affect warfarin metabolism [16]. While using a NOAC will not necessarily improve a patient's compliance with dosing, their pharmacology limits concerns regarding drug–drug and food–drug interactions and the need for routine monitoring [17]. This review discusses current treatment guidelines for AF, provides a brief overview of NOAC pharmacology and the phase III clinical trials for the prevention of stroke and systemic embolic events (SEE), and covers management considerations for patients with AF.

2 Risk Stratification

The three main goals in the treatment of AF are rate control, rhythm control, and managing stroke risk. Following confirmation of AF and determination of stroke risk, patients who require anticoagulation should be evaluated to balance the risk of stroke with the risk of bleeding resulting from antithrombotic therapy. Current American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guidelines recommend risk stratification using the CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥75 years [doubled], Diabetes mellitus, prior Stroke or transient ischemic attack [TIA] or thromboembolism [doubled], Vascular disease, Age 65–74 years, Sex category) scoring system [4, 17] (Fig. 1). CHA_2DS_2-VASc outperforms $CHADS_2$ (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, prior Stroke or TIA or thromboembolism [doubled]) (Table 1) and the ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) score in determining patients for whom there is a truly low thrombotic risk [18–20].

Based on this risk stratification, anticoagulation may be omitted for patients who have NVAF and a CHA_2DS_2-VASc score of 0 [4]. Oral anticoagulants, aspirin, or no treatment may be considered for patients with an intermediate risk of stroke (CHA_2DS_2-VASc score of 1) [4, 21]. Patients with NVAF and a CHA_2DS_2-VASc score ≥2 or who have had a prior stroke or TIA should receive oral anticoagulation, based on current guideline recommendations [4]. Some debate exists regarding the net benefit of anticoagulant treatment in patients with a CHA_2DS_2-VASc score of 1. Differing rates of stroke risk in patients with AF and one additional stroke risk have been reported, suggesting that further determination of critical risk factors in various populations should be assessed [20, 22, 23].

Assessment of the 1-year risk of major bleeding in patients with AF by HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly

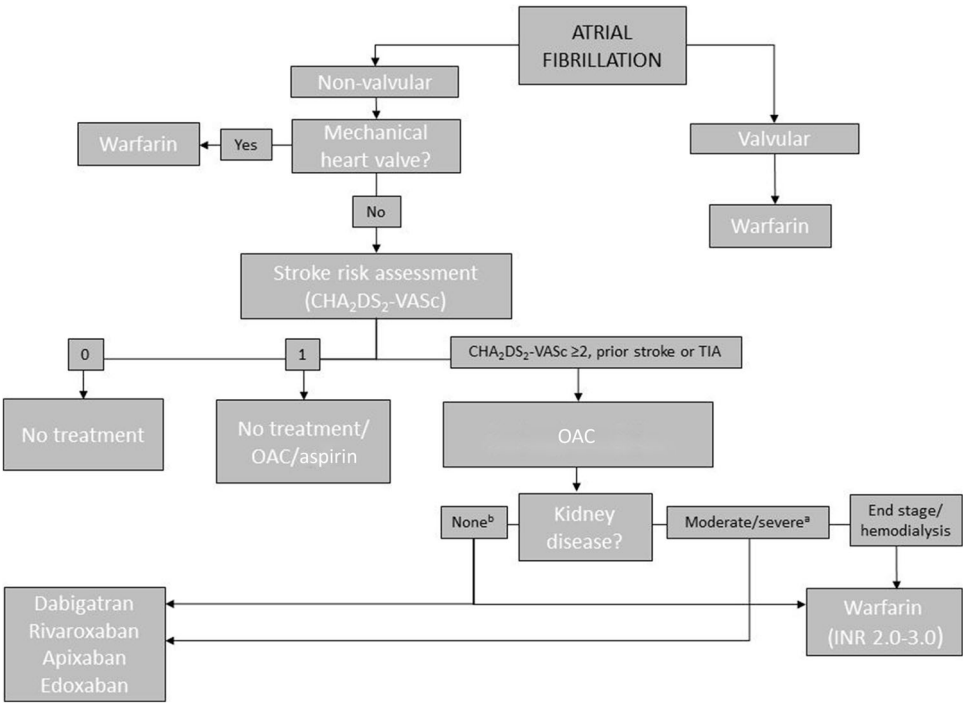

Fig. 1 Flowchart of oral anticoagulant use for stroke prevention based on risk factors [4]. [a]Reduced doses should be considered; safety and efficacy not established. [b]Recommended for patients with trouble controlling INR. *CHA_2DS_2-VASc* congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or TIA or thromboembolism (doubled), vascular disease, age 65–74 years, sex category. *INR* international normalized ratio, *OAC* oral anticoagulation, *TIA* transient ischemic attack

Table 1 Rate of stroke by $CHADS_2$/$CHADS_2$-VASc score and bleeding risk by HAS-BLED score [4, 24]

$CHADS_2$	CHA_2DS_2-VASc
Congestive heart failure	Congestive heart failure
Hypertension	Hypertension
Age ≥75 years	Age ≥75 years (doubled)
Diabetes mellitus	Diabetes mellitus
Prior stroke/TIA/thromboembolism (doubled)	Prior stroke/TIA/thromboembolism (doubled)
	Vascular disease (prior MI, PAD, aortic plaque)
	Age 65–74 years
	Sex (category)

$CHADS_2$	Adjusted rate of stroke/year (%)	CHA_2DS_2-VASc score	Adjusted rate of stroke/year (%)
0	1.9	0	0
1	2.8	1	1.3
2	4.0	2	2.2
3	5.9	3	3.2
4	8.5	4	4.0
5	12.5	5	6.7
6	18.2	6	9.8
		7	9.6
		8	6.7
		9	15.2

HAS-BLED	HAS-BLED score	Bleeding risk (per 100 patient-years)
Hypertension	0	1.13
Abnormal renal and liver function (1 point each)	1	1.02
Stroke	2	1.88
Bleeding	3	3.74
Labile INRs	4	8.70
Elderly	5	12.50
Drugs or alcohol (1 point each)	6	0.0
	7	N/C
	8	N/C
	9	N/C

INR international normalized ratio, *MI* myocardial infarction, *N/C* not calculated, *PAD* peripheral arterial disease, *TIA* transient ischemic attack

[>65 years], Drugs/alcohol concomitantly) [24] is recommended by European Heart Rhythm Association (EHRA), and European Society of Cardiology guidelines, but not AHA/ACC/HRS [4, 25, 26]. To calculate this score, each named clinical characteristic present is assigned 1 point and summed (Table 1) [24]. A HAS-BLED score ≥3 indicates a patient who is potentially at high risk for bleeding events [24]. HAS-BLED demonstrates good predictive accuracy overall, with a better predictive accuracy for patients receiving either no antithrombotic therapy or antiplatelet therapy [24]. In initial validation studies, a score of 1 was associated with a 0.83 % yearly incidence of major bleeding events, whereas a score >5 was associated with an incidence of 16.6 % per year [27]. In patients for whom the risk for thromboembolism and bleeding are both high, a comprehensive management approach would include assessment and modification of extrinsic factors that impact risk. These include adequate control of hypertension (both for thromboembolism and bleeding risk), examination of alcohol intake, and the current use of drugs that could increase risk. Furthermore, it should be noted that in patients with AF who develop gastrointestinal (GI) bleeding while receiving warfarin, restarting warfarin is associated with an overall decreased risk of thromboembolism and mortality without a significantly increased risk of recurrent GI bleeding [28].

3 Pharmacology of Non-Vitamin K Antagonist Oral Anticoagulants (NOACs) Versus Warfarin

Warfarin is relatively inexpensive and readily available, is partially reversible, and has well-understood interactions with other drugs. Warfarin is broadly indicated, and is suitable for patients with mechanical valves [4]. Despite its proven effectiveness, there are several recognized disadvantages of warfarin, including a narrow therapeutic range, drug–drug interactions that can be delayed, food–drug interactions, slow dose-adjustment time, and genetic variability in the enzymes involved in its metabolism, all of which can affect INR [16]. In addition, in order to assure that a therapeutic INR is maintained, frequent patient monitoring is required [4], which some patients may find burdensome. NOACs, which directly inhibit factor Xa (rivaroxaban, apixaban, and edoxaban) or thrombin (dabigatran), were developed to address some of the disadvantages of warfarin. NOACs have a predictable anticoagulant response, making regular laboratory monitoring unnecessary. Anticoagulation with NOACs is achieved quickly, reaching peak plasma concentrations 1–4 h following oral administration, in comparison with the delayed onset of warfarin (Table 2) [29–32]. Half-lives of NOACs are shorter than that of warfarin, and range from 5 to 15 h [29–32]. NOACs have fewer drug–drug and drug–food interactions than warfarin. Although rivaroxaban should be administered with food [12], the other NOACs can be administered without regard to food.

There are disadvantages associated with NOACs. Bleeding risks increase when NOACs are administered with other anticoagulants, platelet inhibitors, or non-steroidal anti-inflammatory drugs. NOACs are substrates of the P-glycoprotein (P-gp) transporter [14, 33–36], and many rate-controlling and anti-arrhythmic drugs interact with P-gp [26]. In addition, the NOACs, to varying degrees, are substrates of cytochrome P450 (CYP) isoenzyme 3A4 [35, 37–39]. As such, co-administration of an NOAC with P-gp inducers or inhibitors and/or CYP3A4 inducers or inhibitors may impact exposure to the NOAC. This is related to the degree to which the NOAC depends on P-gp for transport or on CYP3A4 for metabolism [34, 35]. Thus, verapamil, diltiazem, quinidine, amiodarone, and dronedarone are associated with increased NOAC exposure, and use of these agents may require NOAC dose reduction or may be contraindicated [26] in patients taking NOACs. The lack of laboratory monitoring for NOACs may also be a negative as it is difficult to determine the level of anticoagulation, and compliance can be assessed only by patient feedback and refill frequency [4, 26].

4 Phase III NOAC Clinical Trials

Phase III clinical trials evaluating NOACs are compared in Table 3. These include the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) [40], ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) [41], ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) [42], and the ENGAGE AF-TIMI 48 trial (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction Study 48) [43]. All of these trials included both hemorrhagic and ischemic events in the primary efficacy endpoint of stroke and SEE (Table 3).

Table 2 Non-vitamin K antagonist anti-coagulant pharmacology [11, 12, 34, 39, 44, 45]

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Time to maximal concentration (h)	1–3	2–4	3–4	1–2
Half-life (h)	12–17	5–9	12	10–14
Renal elimination[a] (%)	80	66	27	35
Transporters	P-gp	P-gp/BCRP	P-gp/BCRP	P-gp
Metabolized by CYP450	No relevant effect	Yes	Yes	No relevant effect
Potential drug interactions	P-gp inhibitors in the background of renal impairment and P-gp inducers	Combined P-gp and strong CYP3A4 inhibitors and inducers	Strong dual inhibitors of CYP3A4 and P-gp increase blood levels; strong dual inducers of CYP3A4 and P-gp	Potent inhibitors of P-gp

BCRP breast cancer resistance protein, *CYP3A4* cytochrome P450 isoform 3A4, *P-gp* P-glycoprotein

[a] For dabigatran, based on absorbed dose; for rivaroxaban, apixaban, and edoxaban, based on orally administered dose

Table 3 Key aspects of the non-vitamin K antagonist anti-coagulant phase III clinical trials [40–43]

Trial	Dosing	Design	Patients enrolled (*n*)	Mean $CHADS_2$ score[a]	Median follow-up (years)	Mean percent TTR
RE-LY						
Dabigatran	110 or 150 mg, bid	Non-inferiority, prospective, randomized, open-label for warfarin, blinded for dabigatran	18,113	2.1	2.0	64
Warfarin	Dose adjusted to INR 2.0–3.0					
ROCKET AF						
Rivaroxaban	20 mg od, 15 mg daily in pts with Cl_{Cr} 30–49 ml/min	Non-inferiority, prospective, randomized double-blind, double-dummy, parallel-arm	14,264	3.5	1.9	55
Warfarin	Dose adjusted to INR 2.0–3.0					
ARISTOTLE						
Apixaban	5 mg bid; 2.5 mg bid in pts with ≥2 of the following: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dl (133 μmol/l)	Non-inferiority, prospective, randomized double-blind, double-dummy, parallel-arm	18,201	2.1	1.8	62
Warfarin	Dose adjusted to INR 2.0–3.0					
ENGAGE AF						
Edoxaban	60 or 30 mg od; 50 % dose reduction for pts with a Cl_{Cr} 30–50 ml/min, body weight ≤60 kg, or concomitant treatment with P-gp inhibitors	Non-inferiority, prospective, randomized double-blind, double-dummy, parallel-arm	21,105	2.8	2.8	65
Warfarin	Dose adjusted to INR 2.0–3.0					

bid twice daily, *CI* confidence interval, Cl_{Cr} creatinine clearance, *CRNM* clinically relevant non-major, *INR* international normalized ratio, *od* once daily, *P-gp* P-glycoprotein, *pts* patients, *TTR* time in therapeutic range

[a] In ROCKET AF, INRs calculated 7 days after randomization and during treatment interruptions were excluded from calculation

The NOAC clinical trials cannot be directly compared due to differences in study design and enrolled populations. Notably, RE-LY was a prospective, randomized, open-blinded, endpoint trial, and the other three trials employed a double-blind, double-dummy design. (Table 3). Additionally, the number of tested doses, dose frequency, and patient criteria for their administration differed among the four trials. RE-LY evaluated two doses of dabigatran twice daily, ROCKET AF evaluated one daily dose of rivaroxaban, ARISTOTLE evaluated one twice-daily dose of apixaban, and ENGAGE AF evaluated two once-daily doses of edoxaban, with dose reductions, as described above, allowed in ROCKET AF, ARISTOTLE, and ENGAGE AF [40–43]. RE-LY and ARISTOTLE assessed non-inferiority and superiority in the intention-to-treat population, ROCKET AF assessed non-inferiority in patients who were protocol-compliant on treatment and superiority in the on-treatment and intention-to-treat population, ENGAGE AF assessed non-inferiority in the modified intention-to-treat population, comprising patients who underwent randomization and received at least one dose of study drug, and superiority in the intention-to-treat population [40–43].

Each of the trials required a diagnosis of AF for inclusion in the study, with the exception of ARISTOTLE, which included both AF and atrial flutter [42]. Larger proportions of patients with paroxysmal AF were enrolled in RE-LY (33 %) and ENGAGE AF (25 %) compared with ROCKET AF (18 %) and ARISTOTLE (15 %). Due to differences in $CHADS_2$ score inclusion criteria, patients with higher mean $CHADS_2$ scores were enrolled in ROCKET AF (3.5) and ENGAGE AF (2.8) compared with RE-LY and ARISTOLE (2.1 for both) (Table 4) [40–43].

5 Differences in the NOAC Phase III Trial Outcomes

5.1 Rates of Stroke, Systemic Embolism, and Myocardial Infarction

Overall, the results of the phase III trials indicate that the ability of NOACs to prevent strokes and SEEs is comparable or better than that of warfarin (Table 4). It is important to note that the percent time in therapeutic range (TTR) on warfarin differed between the trials, but was

Table 4 Summary of outcomes from the phase III clinical trials [40–43]

	Stroke or systemic embolism		Ischemic stroke[b]		Primary safety outcome[c]		GI bleeding		Intracranial bleeding	
	Rate[a]	HR *p* value			Rate[a]	HR *p* value	Rate[a]	HR *p* value	Rate[a]	HR *p* value
RE-LY										
Dabigatran	1.53	0.91 (0.74–1.11)	1.34	1.11 (0.89–1.40)	2.71	0.80 (0.69–0.93)	1.12	1.10 (0.86–1.41)	0.23	0.31 (0.20–0.47)
110 mg bid		<0.001		0.35		0.003		0.43		<0.001
Dabigatran	1.11	0.66 (0.53–0.82)	0.92	0.76 (0.60–0.98)	3.11	0.93 (0.81–1.07)	1.51	1.50 (1.19–1.89)	0.30	0.40 (0.27–0.60)
150 mg bid		<0.001		0.03		0.31		<0.001		<0.001
Warfarin	1.69		1.20		3.36		1.02		0.74	
ROCKET AF										
Rivaroxaban	1.70	1.7 (0.66–0.96)	1.34	0.94 (0.75–1.17)	14.90	1.03 (0.96–1.11)	3.20	NR	0.50	0.67 (0.47–0.93)
20 mg od[d]		<0.001		0.581		0.44		<0.001		0.02
Warfarin	2.20		1.42		14.50		2.20		0.70	
ARISTOTLE										
Apixaban	1.27	0.79 (0.66–0.95)	0.97	0.92 (0.74–1.13)	2.13	0.69 (0.60–0.80)	0.76	0.89 (0.70–1.15)	0.33	0.42 (0.30–0.58)
5 mg bid[e]		<0.01[g]		0.42		<0.001		0.37		<0.001
Warfarin	1.60		1.05		3.09		0.86		0.80	
ENGAGE AF										
Edoxaban	1.18	0.79 (0.63–0.99)	1.25	1.00 (0.83–1.19)	2.75	0.80 (0.71–0.91)	1.51	1.23 (1.02–1.50)	0.39	0.47 (0.34–0.63)
60 mg od[f]		<0.001		0.97		<0.001		0.03		<0.001
Edoxaban	1.61	1.07 (0.87–1.31)	1.77	1.41 (1.19–1.67)	1.61	0.47 (0.41–0.55)	0.82	0.67 (0.53–0.83)	0.26	0.30 (0.21–0.43)
30 mg od[f]		0.005		<0.001		<0.001		<0.001		<0.001
Warfarin	1.50		1.25		3.43		1.23		0.85	

bid twice daily, *HR* hazard ratio vs. warfarin, *NR* not reported, *od* once daily

[a] RE-LY, ARISTOTLE, and ENGAGE AF-TIMI-48—annualized event rate; ROCKET AF—events per 100 patient-years

[b] RE-LY—ischemic or non-specified stroke; ARISTOTLE—ischemic or uncertain type of stroke

[c] RE-LY, ARISTOTLE, and ENGAGE AF-TIMI-48—major bleeding; ROCKET AF—major and nonmajor clinically relevant bleeding

[d] Patients with a Cl_{Cr} 30–49 ml/min received 15 mg daily

[e] Patients with ≤2 of the following: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL (133 μmol/l) received a dose of 2.5 mg bid

[f] A 50 % dose reduction was given for patients with a Cl_{Cr} 30–50 mL/min, body weight ≤60 kg, or concomitant treatment with P-glycoprotein inhibitors

[g] For superiority

higher than a reported mean US-based "real-world" TTR of 53.7 % [46], for all clinical trials with the exception of ROCKET, and the highest mean TTR was achieved in the ENGAGE AF trial (Table 3). Rates of ischemic stroke were similar in trials for rivaroxaban and apixaban relative to warfarin; dabigatran 150 mg was associated with a lower rate of ischemic stroke relative to warfarin, although the 110-mg dose resulted in a similar rate relative to warfarin [40–42]. Rates of ischemic stroke were similar to those for warfarin for the high-dose edoxaban regimen, but more frequent with the low-dose edoxaban regimen [43]. Each NOAC provided significantly greater reductions in the risk for intracranial bleeding compared with warfarin.

In ROCKET AF, patients with a history of myocardial infarction (MI) tended to have worse cardiovascular and bleeding outcomes than patients without a history of MI [47]. Rates of intracranial hemorrhage (ICH) and fatal bleeding associated with rivaroxaban use were lower compared with warfarin in both patients with and without a history of prior MI [47]. Rates of MI were not significantly different between patients treated with apixaban and warfarin [42] or in patients treated with edoxaban compared with warfarin [43]. Although rates of MI were initially reported as significantly increased by dabigatran [40], this trend has not persisted in later analyses, in which the MI rate was similar to that with warfarin [48].

5.2 Bleeding Rates

Overall, the results of the phase III trials indicate that rates of major bleeding or major bleeding and clinically relevant non-major (CRNM) bleeding with NOACs are comparable or better than with warfarin (Table 4). Rates of major bleeding were similar between dabigatran 150 mg and warfarin, although rates of major bleeding were significantly reduced with dabigatran 110 mg [40]. Likewise, rates of the composite of major bleeding and CRNM bleeding were similar between rivaroxaban and warfarin [41]. Rates of major bleeding were significantly reduced relative to warfarin for apixaban and both dosing regimens of edoxaban [42, 43].

Approximately 10 % of all cases of ICH occur in patients receiving warfarin [49]. Warfarin is associated with a reduced risk of thromboembolism compared with no therapy, and a 31 % reduction in all-cause mortality, but increases the risk of ICH twofold [50]. The NOACs perform significantly better than warfarin in reducing intracranial bleeding risks. In each NOAC phase III trial, intracranial bleeding rates were significantly decreased relative to warfarin for all drugs and doses [40–43] (Table 4). Compared with warfarin, apixaban reduces the risk of a first major hemorrhage by 31 % and is associated with fewer ICHs, fewer trauma-associated hemorrhages, and a 50 % reduction in major hemorrhage leading to death within 30 days of the event [51]. In a subanalysis of RE-LY, 154 ICHs occurred in 153 patients, with an overall 30-day mortality rate of 36 %. Patients who suffered an ICH tended to be older, with a history of stroke or TIA, more likely to have taken aspirin, less likely to have heart failure, and more likely to have a lower estimated creatinine clearance (Cl_{Cr}) [52]. Lower rates of ICH, fatal ICH, and subdural hematoma were noted in the patients receiving dabigatran compared with warfarin [52]. Both the higher- and lower-dose once-daily edoxaban regimens are associated with significant reductions in various subtypes of intracranial bleeding compared with warfarin [53]. Fewer numbers of ICHs are projected to result in fewer clinical events, reduced stroke severity, and lower treatment and follow-up-related costs for patients treated with NOACs [54].

In general, the NOACs are associated with an increased risk for GI bleeding; however, the risk varies across drugs [10]. Dabigatran 150 mg is associated with higher rates of GI bleeding than warfarin, whereas GI bleeding rates for dabigatran 110 mg do not significantly differ from warfarin [40]. This latter dose has not been approved in the USA, but has been approved for use in Canada and the EU [55, 56]. Although there have been many postmarketing reports of serious and fatal bleeding events associated with dabigatran, bleeding rates associated with dabigatran do not appear to be higher than those associated with warfarin based on an analysis of insurance-claim data and administrative data from the US FDA Mini-Sentinel Database [57]. However, other analyses confirm greater rates of GI bleeding associated with dabigatran [58]. GI bleeding rates are increased for rivaroxaban compared with warfarin [41]. Apixaban has not been shown to have significantly different GI bleeding rates compared with warfarin [42]. High-dose edoxaban results in more frequent GI bleeds than warfarin; however, low-dose edoxaban results in fewer GI bleeds relative to warfarin (Table 4) [10].

6 Additional Analyses

6.1 Clopidogrel/Aspirin

In AVERROES (Apixaban vs. Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients who have Failed or are Unsuitable for Vitamin K Antagonist Treatment), apixaban was superior to aspirin for stroke prevention and carried a similar bleeding risk. Roughly 1 year after treatment, fewer patients who received apixaban than patients who received aspirin were hospitalized for cardiovascular reasons [59]. This reduction was driven primarily by fewer stroke-related hospitalizations.

In a subanalysis of RE-LY examining concomitant antiplatelet use and dabigatran or warfarin use, the risks of major bleeding were higher for patients receiving dual antiplatelet therapy than only a single antiplatelet medication [60]. The efficacy and safety of dabigatran was similar for patients receiving antiplatelet therapy with dabigatran compared with patients receiving dabigatran only. However, this subanalysis was not statistically powered for comparisons, and more studies of these interactions would be beneficial. The efficacy and safety of apixaban was not different between patients with or without concomitant aspirin use in the ARISTOTLE trial [61]. In a subanalysis of ENGAGE AF, both low- and high-dose edoxaban regimens had similar efficacy but significantly reduced major bleeding compared with warfarin in patients receiving concomitant antiplatelet medication [62].

6.2 NOACs and Cardioversion/Ablation

Thromboembolic risk around the time of cardioversion can be reduced by appropriate anticoagulation management [4]. As warfarin has a delayed onset of action, patients may require bridging therapy with heparin or low-molecular-weight heparin (LMWH) if a therapeutic INR range is not achieved or if a patient is new to VKA. On the other hand, due to their rapid onset, the use of NOACs may potentially be advantageous for this procedure.

Most studies examining cardioversion and NOAC use have been small and generally have not been sufficiently powered for statistical analysis. Patients undergoing electrical cardioversion, pharmacologic cardioversion, or catheter ablation who received continuous rivaroxaban treatment had similar numbers of incidents of stroke or systemic embolism and similar rates of major or CRNM bleeding compared with patients treated with warfarin during cardioversion [63]. In a prospective, randomized clinical trial of patients undergoing cardioversion, similar rates of the composite of stroke, TIA, peripheral embolism, MI, and cardiovascular death and major bleeding were associated with rivaroxaban and warfarin, as well as similar rates of major bleeding [64]. Rivaroxaban was also associated with a significantly shorter time to cardioversion than was warfarin [64]. Clinical events occurring after cardioversion for AF were comparable in patients who had received apixaban and warfarin at randomization; event rates were small and did not differ for patients receiving continuous administration of study drug [65]. Among patients undergoing cardioversion receiving dabigatran 110 mg, dabigatran 150 mg, or warfarin, rates of stroke and SEE within 30 days of the procedure were low [66]. Some studies have shown increases in thromboembolic complications including stroke and TIA following periprocedural use of dabigatran for AF ablation, yet other studies have not shown any increase in risk [67, 68]. Additional studies on the use of NOACs for cardioversion and ablation are ongoing.

6.3 Atrial Fibrillation and Transient Ischemic Attack/Heart Failure

Only a few subanalyses have examined the use of NOACs for stroke prevention in AF patients with heart failure or prior TIA. Apixaban had efficacy and safety superior to that of warfarin for patients with AF and left ventricular systolic dysfunction and heart failure-preserved ejection fraction, with the greatest absolute benefits in the highest risk patients with left ventricular systolic dysfunction [69]. No differences in treatment-related outcomes were shown between patients with previous stroke or TIA for dabigatran compared with warfarin, with the exception of vascular death [70]. Dabigatran, rivaroxaban, and edoxaban have shown consistent effects relative to warfarin for patients with heart failure compared with patients without heart failure [71, 72].

7 Patient Management

Transitions between NOACs should be managed in accordance with label instructions, individual patient characteristics, and the half-life and speed of onset of each NOAC [73]. When transitioning from a NOAC to warfarin, treatment with warfarin should be overlapped with the NOAC to allow effective levels of anticoagulation to be reached [25], with INR monitored until a stable level of 2–3 has been achieved [26]. Initiation of warfarin treatment requires daily checks until a therapeutic range of 2.0–3.0 has been reached and sustained for 2 consecutive days. When switching from warfarin to an NOAC, the INR should be adjusted to an INR <2 for patients who will receive dabigatran or apixaban, ≤ 2.5 for patients who will receive edoxaban, or <3 for patients who will receive rivaroxaban prior to NOAC administration, to prevent excessive anticoagulation [11–14].

Boxed warnings have been issued for dabigatran, apixaban, edoxaban, and rivaroxaban due to an increased risk of thromboembolic events following treatment discontinuation [11–14]. Continued anticoagulation is recommended for these patients unless pathological bleeding prompted discontinuation; coverage with another anticoagulant should be provided if patients discontinue for reasons other than pathological bleeding [11–14].

Since the NOACs have short half-lives, it is important that patients are properly educated regarding their use, as

missing a dose could negatively affect anticoagulation. Cessation of anticoagulant therapy has been associated with high rates of stroke, SEE, and all thrombotic events [74]. These concerns highlight the importance of education for all patients taking anticoagulants.

7.1 Peri-Procedural Management

Recommendations call for discontinuation of warfarin therapy 5 days prior to surgery for elective procedures [75]. Patients with AF at a high risk of thromboembolism should be given bridging therapy with heparin [75]. The majority of interventions do not require bridging with LMWH [4, 26]. NOACs can be discontinued 24 and 48 h before procedures associated with risk of minor and major bleeding, respectively [4, 26]. Apixaban or rivaroxaban should be discontinued 36 h prior to low-risk procedures for patients with kidney dysfunction (Cl_{Cr} 15–30 ml/min) [26]. The time necessary for dabigatran discontinuation prior to procedures is graded by renal function, with longer times recommended prior to procedures for patients with greater degrees of renal impairment [26]. Therapy with NOACs can be reinitiated following surgery once effective hemostasis is achieved. Interventions to stabilize patients who are hemodynamically unstable and require emergency cardioversion should not be delayed due to initiation of anticoagulation [4].

7.2 Management of Bleeding

No quantitative tests of anticoagulation exist for the NOACs; however, qualitative levels of NOAC anticoagulation can be assessed if the time of last dose of anticoagulant is known. The decision to discontinue or reverse anticoagulation should be made in consideration of the time sensitivity of the clinical situation [73]. Reversal of warfarin can be achieved with administration of vitamin K, fresh frozen plasma, or coagulation factors [76]. Currently, the NOACs lack specific reversal agents. Prothrombin complex concentrate (PCC) infusion reverts thrombin generation-endogenous thrombin potential to near baseline values and reverses rivaroxaban-induced increased prothrombin time [77, 78]. PCC infusion also reverses the effects of edoxaban on endogenous thrombin potential, but not prothrombin time [79, 80]. The use of activated PCC, factor VIII inhibitor bypassing activity, and an active recombinant form of factor VII [78, 81, 82] have also been assessed as reversal agents; however, these drugs were developed as hemostatic agents for bleeding and bleeding deficiencies, not for reversal of direct FXa or IIa inhibition [83, 84]. The synthetic small-molecule PER977 [85, 86], catalytically inactive human recombinant FXa andexanet alfa (PRT064445) [87], and an antibody fragment specific to dabigatran [88] are also under investigation as specific reversal agents.

A total of 87–95 % of rivaroxaban and apixaban bind plasma proteins, 35 % of dabigatran, and 40–59 % of edoxaban is protein bound [12, 14, 31, 89]. The low protein binding of dabigatran allows it to be removed by dialysis, as recommended by the package insert, although this may not be feasible in unstable patients. Dialysis is not effective for removal of rivaroxaban [12] edoxaban [13], or apixaban [14].

7.3 Specific Populations

7.3.1 Renal Impairment

Consideration of renal function is important prior to initiation of NOAC treatment. Although the renal clearance of NOACs vary, patients with renal impairment may require dose reduction to avoid increased plasma concentrations of NOACs [4, 90–92]. Of the NOACs, dabigatran is the most dependent on renal function, with >80 % of the dabigatran dose that is absorbed excreted in urine [37]. Rivaroxaban, edoxaban, and apixaban have less renal dependence, and are excreted via urine by 66, 50, and 27 %, respectively [12–14]. AF patients with mild or moderate renal impairment (Cl_{Cr} 30–49 ml/min) may receive dabigatran 150 mg twice daily [11]. A reduced dose of 75 mg twice daily is recommended for patients with a Cl_{Cr} 15–30 ml/min [11]; however, these patients were not included in the randomized clinical trial. Rivaroxaban is not recommended in patients with a Cl_{Cr} <15 ml/min, and renal function should be monitored in all patients receiving the drug. Patients who have any two of age ≥80 years, body weight ≤60 kg, or elevated serum creatinine (≥1.5 mg/dl) should receive an adjusted dose of apixaban 2.5 mg twice daily [14]. Edoxaban doses should be reduced to 30 mg once daily in patients with a Cl_{Cr} 15–50 ml/min [13]. Edoxaban should not be used in patients with a Cl_{Cr} >95 ml/min [13].

Generally, bleeding rates with NOACs are similar or reduced relative to warfarin in patients with renal impairment. Major bleeding rates for dabigatran 110 and 150 mg were similar to warfarin in this patient group [93]. Patients with Cl_{Cr} ≤50 ml/min receiving apixaban had more significant reductions in major bleeding than those with higher Cl_{Cr}, even after adjusting for patients who received a reduced dose of 2.5 mg twice daily [94]. Less critical organ bleeding and fatal bleeding occurred with rivaroxaban 15 mg compared with warfarin in patients with Cl_{Cr} 30–49 ml/min [95, 96]. In a prespecified post hoc analysis of ENGAGE AF, patients with a Cl_{Cr} 30–50 ml/min experienced fewer adjudicated major bleeding events compared with warfarin [13].

7.3.2 Aged Patients

Hemorrhage risk increases with prior stroke and GI bleeding, hypertension, concomitant use of antiplatelet medication, anemia, renal insufficiency, the presence of cerebrovascular disease, and malignancy, all of which may be more common in the elderly [97]. Further, elderly patients are more likely to take multiple medications and may not receive sufficient patient education. However, advanced age should not be seen as a contraindication to oral anticoagulant treatment [98]. Warfarin significantly reduces stroke risk in the elderly, and reduces the risk of ischemic stroke compared with aspirin [97]; however, the risk of major hemorrhage increases with age [99].

In general, the NOACs demonstrated similar efficacy and safety in patients aged ≥75 compared with those aged <75 years [10]. Rates of stroke or SEE are reduced relative to warfarin and are associated with a lower risk of bleeding in phase III trials [41–43]. Older age also had no impact on the efficacy or safety of edoxaban, rivaroxaban, or apixaban compared with younger patients [41–43]. Rates of stroke for patients aged ≥75 years compared with younger patients were not reported for dabigatran; however, dabigatran showed a significant interaction of age by treatment, with both dabigatran 110 mg and dabigatran 150 mg producing a higher risk of major bleeding in patients aged ≥75 years compared with those aged <75 years [100]. Compared with warfarin, edoxaban decreased the absolute risk of major bleeding, including ICH, in elderly patients [101].

7.4 Dosing Recommendations with Certain Concomitant Medications

Both rivaroxaban and apixaban are metabolized via CYP3A4 [12, 14]. Dabigatran is not a CYP3A4 substrate [37], and the metabolites of edoxaban generated by CYP3A4 activity account for <5 % of edoxaban exposure [13]. Due to these considerations, apixaban should be given at a reduced dose or concomitant use should be avoided in patients who are also taking strong P-gp and CYP3A4 inhibitors [14]. Dabigatran should be given at a reduced dose to patients with moderate renal impairment who are taking P-gp inhibitors [11], and rivaroxaban should not be administered to patients taking combined P-gp and strong inducers and inhibitors of CYP3A4 [12]. No edoxaban dose reductions are required for concomitant P-gp inhibitor use or CYP3A4 in patients with NVAF [13]. The concomitant use of edoxaban with rifampin, a strong P-gp inducer, should be avoided [13].

8 Conclusions

In clinical trials, NOACs have demonstrated comparable or better risk reductions for stroke and SEE and for bleeding compared with warfarin. In particular, they all significantly reduce the risk for ICH. Patients treated with NOACs are projected to have fewer clinical events and reduced stroke severity, primarily due to fewer numbers of ICHs. Further, the use of NOACs provides more options for specific patient groups, depending on their characteristics and concomitant medications. The risk of GI bleeding should be taken under consideration for patients receiving NOACs; however, some patient populations may benefit greatly from the use of NOACs over traditional warfarin therapy.

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