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THE SAFETY OF NEW ORAL ANTICOAGULANTS FOR ISCHEMIC STROKE AND SYSTEMIC EMBOLISM PREVENTION IN FEMALES WITH ATRIAL FIBRILLATION

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ABSTRACT

The prevalence of atrial fibrillation is lower in females than in men, but the risk of stroke and systemic thromboembolism is comparable or even higher. Administration of anticoagulant therapy does not modify this difference. Two classes of non-vitamin K antagonist oral anticoagulants were studied in atrial fibrillation: direct thrombin inhibitors, like Dabigatran, and activated factor X inhibitors, like Rivaroxaban, Apixaban and Edoxaban. Response to oral anticoagulants could differ between the gender. This medication was evaluated in phase III randomized controlled trials. Non-vitamin K antagonist oral anticoagulants have been proved more efficacious than Warfarin for stroke and systemic embolism prevention in women, but conclusions regarding the safety and the bleeding are heterogeneous. As in men, before prescribing a NOAC to a female with AF, the stroke and the bleeding risk have to be carefully estimated. It is important that future studies to be targeted on comparison between of non-vitamin K antagonist oral anticoagulants versus Warfarin in females with non-valvular atrial fibrillation

Keywords: non-VKA oral anticoagulants, atrial fibrillation, females, safety

Abbreviations

AF – atrial fibrillation
CKD – chronic kidney disease
CrCl – creatinine clearance
CYP3A4 – cytochrome P450 3A4
Factor Xa – activated factor X
GI – gastrointestinal
ICH – Intracranial hemorrhages
INR: International normalized ratio
NOACs – non-VKA oral anticoagulants
P-gp – permeability glycoprotein
TTR – time into therapeutic range
VKAs – vitamin K anticoagulants

INCIDENCE AND PREVALENCE OF ATRIAL FIBRILLATION

The risk of stroke in patients with atrial fibrillation (AF) is approximately 20-30% of all strokes [1,2]. The incidence of AF roughly doubled for every 10-year in the Framingham Heart Study. AF is 1.2 times more frequent in men compared to women [3]. Framingham Heart Study enrolled 5,209 patients (2,336 men and 2,873 women), 30-62 years of age [3]. This study reported that arterial hypertension, diabetes, congestive heart failure, coronary artery disease, and valvular heart disease were independent risk factors for AF [3]. The prevalence of AF ranged between 0.5 and 1% in developed countries and increases with age. The prevalence between 50 and 59 years is 0.5% and rises to 9% between 80 and 89 years [4,5].

In 1998, investigators from the Framingham Heart Study established that AF increased mortality. They reported a 1.5-fold increase in the men's risk of death and 1.9-fold in women, adjusting for clinical risk factors [3].

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Women have a lower prevalence of AF at every age compared with men [8,11], but early trials reported higher rates of thromboembolic events in women compared to men [6].

AF AND STROKE IN WOMEN

The link between female sex and stroke varies across populations and age groups [11,12].

In the ATRIA study, young women (under 65 years of age) had a lower risk of stroke than men. In older age (≥ 75 years), the risk was 10-20% higher than in men of similar age and was not affected by the use of Warfarin [9]. The trial results suggested that the female gender is a risk factor for stroke, closely linked to age and other major risk factors [9-11].

The women aged < 65 years with 'lone' AF have a low annual risk for stroke; therefore, the current European and American guidelines do not recommend anticoagulation therapy for this group [12,13]. In a meta-analysis of 30 studies with 4371714 participants, Edim CA and al. found AF to be a significant risk factor for death and cardiovascular disease, more important in women than in men [14]. When AF associates with stroke, cardiac events, and heart failure, all causes mortality, is more pronounced in women than men [8,13], suggesting that women and men experience risk factors for cardiovascular disease differently [8,15]. It is unclear what could cause these differences. Response to oral anticoagulants could also differ between genders. Some studies revealed a higher risk of bleeding in women [16].

Gender-related differences in the incidence of stroke due to AF ranges from 20% to 70% across the studies and persists after correction for age, risk factors, co-morbidities, and the use of oral anticoagulation [16]. A meta-analysis of 17 reports, which included five randomized controlled trials and 12 prospective observational studies, has shown a 1.3-fold greater risk of AF-related stroke in women, which has not been modified by anticoagulation therapy [17].

The exact mechanism by which female gender may affect predisposition to stroke is not clearly understood [14]. The possibilities are genetics, vascular physiology, and endothelial function. Hormonal influences which modulate the expression of tissue factors are also involved. Other factors are biomarkers linked to prothrombotic processes, factors promoting hypercoagulability. Some studies quote less optimal treatment of underlying cardiovascular disease in females [18]. Hormone replacement therapy may also increase the risk of stroke in women with AF [13,18]. The reasons for the differential effect of gender on stroke rates in older women are multifactorial [13,18]. The studies described increased amyloid production linked to estradiol metabolism. The prevalence of amyloid atrial cardiomyopathy is higher in older women compared to older men. The explanation could be an arrhythmogenic substrate, which would promote the thromboembolism [13,18]. Isolated atrial amyloidosis is found in >90% of old females, facilitated by AF duration [13,18].

SYSTEMIC THROMBOEMBOLISM PREVENTION IN FEMALES WITH AF

Oral anticoagulant therapy is the cornerstone of stroke prevention in patients with AF [19,20].

The non-vitamin K antagonist oral anticoagulant (NOACs) overcome the limitations of using Warfarin in stroke prevention in this group of patients [19,20]. There are two classes of NOACs: direct thrombin inhibitors, such as Dabigatran, and activated factor X (factor Xa) inhibitors, such as Rivaroxaban, Apixaban, and Edoxaban [20].

PHARMACOKINETIC OF NOACS

DABIGATRAN is a reversible competitive inhibitor of thrombin [20]. Mechanism of action is specifically inhibition of free and bound thrombin cloth and thrombin-induced platelet activation inhibition. The kidneys excrete 80% of Dabigatran. In consequence, half-life and dosing are kidney function and creatinine clearance (CrCl) dependent [20].

RIVAROXABAN is an inhibitor of factor Xa, resulting in a blockade of intrinsic and extrinsic coagulation pathways. Elimination is through renal and digestive routes [20].

APIXABAN is a reversible inhibitor of free and bound factor Xa. The principal modes of elimination of Apixaban are both digestive (56%) and renal (24.5%) [20].

EDOXABAN inhibits competitive factor Xa, leading to a reduction in thrombin generation and

thrombus formation. The doses have to adjust in patients with renal impairment [21].

CLINICAL TRIALS WITH NOACS

Large clinical trials evaluated the NOACs [21].

RE-LY (Randomized Evaluation of Long-term Anticoagulation TherapY) was a prospective, randomized controlled, open-labeled trial that compared the efficacy and safety of 110 mg and 150 mg doses of Dabigatran to Warfarin (INR 2-3) [21]. 18,113 patients were enrolled. Primary endpoints were stroke and systemic embolisms. The dose of 110 mg Dabigatran (1.53% events/year) was non-inferior ($p < 0.001$) to Warfarin and the dose of 150 mg Dabigatran (1.1% events/year) was superior to Warfarin ($p < 0.001$) [21]. The rate of major and life-threatening bleeding in the group of 150 mg doses of Dabigatran was similar to Warfarin (3.11% vs. 3.36% events/year, respectively, $p = 0.31$). The 110mg dose of Dabigatran was associated with a 20% risk reduction (2.7% vs. 3.4% events/year, $p = 0.003$) [21]. Intracranial hemorrhages (ICH) were significantly lower in both Dabigatran arms (110 mg BID and 150 mg BID) than it was in Warfarin arm (0.23%, 0.35%, and 0.74% events/year respectively, $p < 0.001$ for both groups) [21]. 150 mg dose of Dabigatran increased the risk for gastrointestinal (GI) bleeding when compared to Warfarin (1.51% and 1.02% respectively, $p < 0.001$), and the 110 mg dose of Dabigatran was similar to Warfarin (1.12% and 1.02% respectively, $p = 0.43$). The risk of bleeding with Dabigatran depended on age. Age >75 years is also directly related to the risk of strokes and bleeds in AF patients [21].

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) was a prospective, randomized, double-blind trial, which compared Rivaroxaban and Warfarin in patients with nonvalvular AF [22]. 14,264 patients were enrolled. Patients were randomized to receive 20 mg/day doses of Rivaroxaban (15 mg/day if the creatinine clearance is 30-49 ml/min) or Warfarin (target INR: between 2 and 3) [22]. The primary endpoints were stroke and systemic embolism. ROCKET AF trial enrolled patients with a higher risk of stroke than other trials with NOACs [13]. Rivaroxaban was non-inferior to Warfarin with respect to the primary endpoint (2.1% vs. 2.4% respectively, for non-inferiority $p < 0.001$) [22]. There was no difference between the rates of major and clinically significant non-major bleeding rates between Rivaroxaban and Warfarin groups (14.9% vs. 14.5% events, respectively p = non-significant). In addition, the rate of ICH was significantly lower in the Rivaroxaban group (0.5% and 0.7% events/year, $p = 0.02$) [22].

ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) study enrolled 18,201 patients with nonvalvular AF. They received Apixaban (5 mg, twice a day) or Warfarin [23]. Stroke and systemic embolism occurred at a rate of 1.25% events per year in the Apixaban group and 1.60% per year in the Warfarin group (HR = 0.79; 95% CI: 0.66-0.95; $p = 0.01$) [23]. Patients in this study who had two or more of the following risk factors: age ≥ 80 years, body weight ≤ 60 kg, or a serum creatinine level ≥1.5 mg per deciliter, were treated with 2.5 mg Apixaban BID (instead of 5 mg BID). The primary composite endpoint, stroke or systemic embolism, occurred in 1.27% patients in the Apixaban arm and 1.6% patients in the Warfarin arm ($p<0.001$ for non-inferiority, $p = 0.01$ for superiority). According to the results, Apixaban was superior to Warfarin in preventing stroke and systemic embolisms in patients with nonvalvular AF and also in all-cause mortality (3.52% vs. 3.94%, $p = 0.047$) [14]. Rates *of* major bleeding events *i*n Apixaban and Warfarin groups were similar, but, unlike other NOACs, GI bleeding rate did not increase with Apixaban relative to Warfarin [14]. Major bleeding occurred less in the Apixaban arm (2.13%) than the Warfarin arm (3.09%) ($p < 0.001$). The ICH rate was 0.33% event/year in the Apixaban group and 0.80% event/year in the Warfarin group ($p < 0.001$) [23].

AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) was a double-blind, randomized trial including 5,599 patients with AF for whom vitamin K antagonist therapy was inappropriate [24]. The patients received Apixaban (5 mg, twice a day) or Aspirin (80–325 mg). The rate of stroke or systemic embolism was 1.6% in the Apixaban group and 3.7% in the Aspirin group (HR 0.45, 95% CI 0.32-0.62, $p < 0.001$) [24]. The

trial early terminated because it demonstrated a significant benefit of Apixaban vs. Warfarin. There was no significant difference in major bleeding rates between Apixaban and Aspirin groups. Patients tolerated Apixaban better than Aspirin [24].

ENGAGE AF TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48) was a randomized, double-blind trial comparing Edoxaban vs. Warfarin for thromboembolism and stroke prophylaxis in nonvalvular AF [25]. 21,105 subjects were randomized to a dose of 60 mg daily (30 mg daily of Edoxaban if any of the following characteristics were present: reduced CrCl**:** 30-50 m/min, bodyweight < 60 kg, or concomitant use of Verapamil, Quinidine, or Dronedarone). The primary endpoint was systemic embolism and stroke. The primary endpoint annual rate was 1.50% with Warfarin when compared to 1.18% with 60 mg Edoxaban ($p = 0.001$ for non-inferiority) and 1.61% with 30 mg Edoxaban ($p = 0.005$ for non-inferiority) [25]. The annual rate of major bleeding was 3.43% in Warfarin, 2.75%, and 1.61% for 60 mg and 30 mg Edoxaban treatment, respectively ($p < 0.001$ for both doses). Both doses of Edoxaban have shown to be as efficient as Warfarin for systemic embolism and stroke prophylaxis in nonvalvular AF. They were associated with significantly lower rates of bleeding and death from cardiovascular causes. On the other hand, GI bleeding rates were significantly higher in Edoxaban 60 mg group than the Warfarin group. (1.51% vs 1.23%; $p = 0.03$) [25]. Overall, Edoxaban's major bleeding rates are lower than Warfarin's, although the high-dose Edoxaban (60 mg/day) had higher GI bleeding rates than Warfarin [25].

FEMALES IN CLINICAL TRIALS WITH NOACS

The risk of AF varies according to clinical and demographic characteristics [26]. Patients with AF are at a 5-6 higher risk of stroke than those in sinus rhythm, especially females [12,14,15].

The proportion of women in trials with NOACs was approximately 40% [26] (Table 1). 6,599 (36.4%) women were enrolled in RELY trial: 2.150 (35.7%) received 110 mg Dabigatran and 2.236 (36.8%) 150 mg Dabigatran. 2.213 (36.7%) of women received Warfarin. NOACs showed similar or superior efficacy in stroke prevention compared to Warfarin, but the stroke rate remains higher in women than in men [27] (Table 2).

TABLE 1. *Women in clinical trials with NOACs*

	RE-LY	ROCKET	ARISTOTLE	AVERROES	ENGAGE AF TIMI 48
Women	6,599 (36.4%)	5,663 (39.7%)	6,416 (35.3%)	2,321 (41%)	8,040 (38%)
Age	71.5	73	70		
Mean CHADS2	2.1	3.5	2.1		2.8
Mean follow up	2 years	707 days	1.8 years	year	2.8 years
TTR%	64	65	62		64

TTR: time into therapeutic range

TABLE 2. *Embolic events in women in clinical trials with NOACs*

TRIAL	Drug/dose	Event rates (%/year) women / men
RELY	Warfarin Dabigatran 150 mg Dabigatran 110 mg	2.03 / 1.49 1.14 / 1.10 1.86 / 1.35
ROCKET- AF	Warfarin Rivaroxaban	5.07 / 3.83 4.5 / 3.34
ARISTOTLE	Warfarin Apixaban	1.8 / 1.5 1.4 / 1.2
AVERROES	Aspirin Apixaban	3.99 / 2.28 1.55 / 0.82
ENGAGE TIMI 48	Edox 60 mg Edox 30 mg	1.76 / 1.45 2.32 / 1.86

In an analysis from the RE-LY trial, women had a more significant relative risk reduction than men. The rate of major bleeding and ICH were not different between males and females [28]. Plasma concentrations of Dabigatran in female subjects were ≈30% higher than in male subjects [28]. The authors concluded that the risks of major bleeding and ischemic stroke related to Dabigatran concentrations. They did not mention sex differences in the association with the outcomes [28].

A population-based cohort study conducted by Tsadok et al. in Canada between 1999 and 2013 aimed to compare sex differences in use, safety, and effectiveness of Dabigatran in patients with AF [28]. The cohort comprised 31,786 women (50.4%) and 31,324 men (49.6%). The median follow-up was 1.3 years. Women had a higher baseline stroke risk and lower baseline bleeding risk compared with men. Mean CHA2DS2-VASc score was higher in women than men (3.9±1.3 versus 2.6±1.4; $p < 0.001$) [28]. Women filled more pre-

scriptions for the lower Dabigatran dose (adjusted OR, 1.35; 95% confidence interval, 1.24-1.48). Dabigatran 150 mg associated with a lower risk of stroke in women (HR 0.79; 95% confidence interval, 0.56-1.04). The incidence of stroke did not differ in both doses of Dabigatran.

Women treated with Dabigatran 110 mg dose had lower bleeding rates, and there was a trend toward lower stroke risk reduction than women taking 150 mg dose Dabigatran [28]. The authors concluded that women might benefit more from treatment with Dabigatran 150 mg for stroke reduction than men because they have a higher baseline risk for stroke [28].

ROCKET trial enrolled 5,663 women (39.7%). The events rate in women with Rivaroxaban was 4.06%/year compare to 5.07%/year in the Warfarin group. The annual rate of bleeding in women was higher with Warfarin compare with Rivaroxaban (19.5 vs. 17.9%) [28].

ARISTOTLE trial randomized 6,416 (35.3%) women with AF. These had a similar rate of stroke or systemic embolism but a lower risk of mortality than men. The clinically relevant bleeding in women was lower than in men. The efficacy and safety of Apixaban compared with Warfarin were consistent for both genders [29]. Events rate with Apixaban was 1.4%/year in women and 1.2%/year in men. The bleeding rate in women was higher with Warfarin than with Apixaban, without gender differences between Apixaban and Warfarin [29].

In a secondary analysis of the AVERROES trial, Lip et al. purposed to assess Aspirin effect compare to Apixaban effect on ischemic stroke and major bleeding in women compared to men. Females had higher ischemic stroke risk when treated with Aspirin compare with Apixaban (1.55 vs. 3.99%/year). The advantage of Apixaban vs. Warfarin was comparable in both sexes [30].

NOACs effect may slightly differ in women, but the differences are clinically negligible [31].

FEMALE GENDER AND RISK OF BLEEDING WITH NOACS

The studies showed that women might have increased NOACs plasma concentrations compared with men. The explanation could be lower body weight or lower CrCl, which would predispose to higher bleeding risk [28,32]. Another cause would be the differences in the coagulation and vascular systems induced by sex hormones [28,32].

A meta-analysis of the ARISTOTLE, AVERROES, RE-LY (150 mg), and ROCKET AF trials reported that women treated with NOACs had lower rates of major bleeding than men (OR 0.84, 95% CI 0.75-0.96, p = 0.007). In the ROCKET AF trial, women receiving Rivaroxaban or Warfarin had a reduced risk of major bleeding compared with men. (HR 0.82, 95% CI 0.70-0.95, p = 0.009) [32]. In the ARISTOTLE trial, females also associated a lower risk of major bleeding compared with men (HR 0.74, 95% CI 0.63-0.87, p = 0.002) [32].

ADVANTAGES AND DISADVANTAGES OF NOACS

Advantages

- rapid onset and offset of action [20]
- absence of dietary interactions [20]
- fewer drug interactions [20]
- simplifying treatment due to predictable anticoagulant effects; this enables administration of fixed doses without the need for coagulation monitoring [20]
- reduction of stroke and systemic embolic events, hemorrhagic stroke, and all cause-mortality

NOACs have a favorable safety profile compared with Warfarin; however, they may associate an increase in gastrointestinal bleeding [20].

Disadvantages

- higher cost [20]
- caution in liver and kidney impairment [20]
- contraindication during pregnancy [20]
- lack of clinical efficacy in thromboprophylaxis in the setting of mechanical valves [20]
- in patients with malignant unwellness and antiphospholipid syndrome [20]

Several factors such as age, race, gender, smoking, and diet can lead to inter-individual variability of NOACs [20]. The presence of common genetic variants or drug-drug interactions may contribute to differences between therapeutic answers [20].

THE AGE AND COMORBIDITIES

Older women (aged ≥75 years) with a previous stroke history and those with renal dysfunction have an increased risk of both ischemic and bleed-

ing events [33]. All patients with AF aged over 75 years are eligible for anticoagulant therapy if their thromboembolic risk is sufficiently high (CHA2DS2–VASc C2) [33]. In old females, guidelines recommend an assessment of risk bleeding using the HAS-BLED score before prescribing NOACS [34].

Chronic kidney disease (CKD) is also a significant limitation for the NOACs prescription in the older woman. AF is present in 15–20% of patients with CKD [36,41]. The patients with AF and CKD have an increased risk of morbidity and mortality due to their excessive risk for both thromboembolic and severe bleeding events [36]. The kidneys partly eliminate the NOACs: Dabigatran: 80%, Rivaroxaban 50%, Apixaban 35%, and Edoxaban 27% [36]. Guidelines usually recommended the Cockroft-Gault formula to estimate CrCl for NOACs dosage. Initial and subsequent monitoring of renal function at least annually is essential [41-43]. Expert consensus documents indicate anti-Xa NOACs instead of VKAs for elderly patients with a glomerular filtration rate of 15-30 ml/min [20,41-43]. NOACs in chronic renal disorder ought to be performed with caution, particularly in aged women with moderate (CrCl 30-50 ml/min) or severe (CrCl 10-30 ml/min) nephropathy [20,36,41-43]. This class of medication should not use in patients with dialysis or with CrCl ≤ 15 ml/min [41,42, 43]. In ARISTOTLE were included patients with a CrCl of 25-29 ml/min [23]. Dabigatran 75 mg twice daily (BID) is approved in the USA, but not in Europe, for patients with an estimated clearance of 15-30 ml/min [21,35]. The USA approved Apixaban 5 mg BID in chronic, stable dialysis-dependent patients [35].

Obese females have a higher risk of developing AF than non-obese patients, with a 4% increase in the risk of AF per unit increase in body mass index. Arterial hypertension, diabetes, and sleep apnea syndrome are often associated with overweight. These factors will further increase the risk of AF [36]. On the other hand, low weight is a bleeding risk factor. Apixaban and Edoxaban dosage should adapt according to weight [41-44].

For weight less than 60 kg, Apixaban should be decreased from 5 to 2.5 mg BID in patients with at least one of age >80 years or serum creatinine greater than 133 mmol/l. Edoxaban dose should be decreased from 60 to 30 mg once daily [41-44].

Advanced liver disease is associated with increased bleeding risk, but is also a prothrombotic disorder [36]. In cases of mild or moderate organ impairment, NOACs can be given with caution, changing the dosage. [41,42,43,44]. In cases of severe organ impairment (Child-Pugh category C) and cirrhotic patients with Child-Pugh category B or C, Rivaroxaban must not be administered [41-44]. Guidelines contraindicate all four NOACs in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including Child-Turcotte-Pugh C cirrhosis [41-44].

RISK STRATIFICATION

Before prescribing a NOAC to a patient with AF, both stroke and bleeding risk have to be estimated [37,41-44].

The American Heart Association/American College of Cardiology/Heart Rhythm Society and the European Society of Cardiology recommend using the CHA2DS2-VASc score to predict stroke risk and guide anticoagulation therapy in individuals with AF [41-44].

European Society of Cardiology guidelines included the CHA2DS2-VASc score in 2010, whereas the American Heart Association/American College of Cardiology guidelines included the score in 2014 [41-44] (Table 3).

The CHA2DS2-VASc score evaluates the risk for stroke and transient ischemic attack (Table 4) [41-44]. This was validated using data from the European Heart Survey trial [37].

CHA2DS2-VASc components are: cardiac failure, arterial hypertension, age ≥75 years (doubled), DM, stroke (doubled), vascular disease, age 65-74, and female gender [37, 38, 39]. Patients with a CHA2DS2-VASc score of 0 have a low risk of ischemic stroke, with an annual stroke rate of approximately 1% or even lower [38]. Some risk factors for thromboembolism are also risk factors for bleeding. These are advanced age, uncontrolled arterial hypertension, history of ischemic heart disease, cerebrovascular disease [37-39].

HAS-BLED score may give prognostic information regarding death and cardiovascular events, not only bleeding risk [40]. The score was first proposed in 2010 after its derivation and validation in the European Heart Survey trial and is recommended by the European Society of Cardiology

guidelines for bleeding risk assessment (Table 5). Score ≥3 necessitates caution and regular review (Table 6) [40,41]. Advanced age, uncontrolled arterial hypertension, ischemic heart disease, cerebrovascular disease, anemia, concomitant antiplatelet therapy, and previous bleeding are predictors of major bleeding events during anticoagulation [40,41]. Labile INR control, advanced patient age, and concomitant aspirin or nonsteroidal anti-inflammatory drug could also predict bleeding during anticoagulant therapy [40,41]. It is important to focus attention on reversible bleeding risk factors [41-44] (Table 7).

TABLE 3. *CHA2DS2-VASC SCORE (according with clinical practice guidelines)*

Risk factor	Score (maximum 9*)
C – Congestive heart failure	1
H – Hypertension	1
A2 – Age75 years or older	2
D – Diabetes mellitus	1
S2 – Stroke, transient ischaemic attack or thromboembolism	2
V – Vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque)	1
A – Age 65 to 74 years	1
Sc – Sex category (i.e. female)	1

** Maximum score is 9; for age, either the patient is 75 years or older and gets two points, is between 65 and 74 and gets one point, or is under 65 years and does not get any points.*

TABLE 4. *Annual risk of stroke after CHA_2DS_2-VASC SCORE calculation (according with clinical practice guidelines)*

CHA_2DS_2-VASC SCORE	Annual risk of stroke
0	0
1	1.3
2	2.2
3	3.2
4	4
6	6.7

TABLE 5. *HAS-BLED SCORE (according with clinical practice guidelines)*

Risk factor	Score (maximum 9*)
H – Hypertension (systolic BP over 160 mmHg)	1
A – Abnormal liver or renal function (1 point each)	1 or 2
S – Stroke	1
B – Bleeding history	1
L – Labile INRs	1
E – Elderly (age over 65 years)	1
D – Drugs* or alcohol (1 point each)	1 or 2

** Concomitant use of drugs that promote bleeding.*
Abbreviations: BP = blood pressure; INR = international normalised ratio

TABLE 6. *Annual risk of bleeding after HAS-BLED SCORE calculation (according with clinical practice guidelines)*

HAS-BLED SCORE	Annual risk of bleeding
0	0.9
1	3.4
2	4.1
3	5.8
4	8.9
5	9.1

The most recent guidelines indications are:

1. The CHA2DS2-VASc score is recommended for stroke risk prediction in patients with AF. (Class I, level A) [43,44].

2. Bleeding risk scores should be considered in AF patients on oral anticoagulation who present risk factors for major bleeding. (Class IIa, level B) [43,44].

3. Oral anticoagulation therapy to prevent thromboembolism is recommended for all females with a CHA_2DS_2-VASc score of 3 or more (I A) or 2 considering individual characteristics and patient preferences (IIa B) [43,44].

4. Patients at low risk (CHA2DS2-VASc score 0) do not benefit from oral anticoagulation therapy therapy and should not be anticoagulated [43,44].

TABLE 7. *Modifiable bleeding risk factors (according with clinical practice guidelines)*

Modifiable bleeding risk factors	Potential modifiable bleeding risk factors	Non-modifiable bleeding risk factors	Biomarker- based bleeding risk factors
Hypertension (especially when systolic blood pressure is > 160 mmHg) Labile INR or time in therapeutic range <60%a in patients on vitamin K antagonists Medication predisposing to bleeding, such as antiplatelet drugs, nonsteroidal anti-inflammatory drug Excess alcohol (≥8 drinks/ week)	Anaemia Impaired renal function Impaired liver function Reduced platelet count or function	Agee (> 65 years), (≥ 75 years) History of major bleeding Previous stroke Dialysis-dependent kidney disease or renal transplant Cirrhotic liver disease Malignancy Genetic factors	High-sensitivity troponine Growth differentiation factor-15 Serum creatinine / estimated CrCl

5. NOACs (Apixaban, Dabigatran, Edoxaban, or Rivaroxaban) are recommended in preference to VKAs (I A) [43,44].

6. The individual patient profile needs to be considered; for example, the renal function needs to be assessed more frequently in older patients (≥75 years), frail patients, intercurrent condition (such as infection or cancer), which may affect hepatic or renal function [43,44].

7. Stroke risk and bleeding risk factors should be periodically reassessed [43,44].

As mentioned before, correcting and minimizing modifiable risk factors is of critical importance to minimize the risk of bleeding while on treatment with a NOAC [43,44].

Guidelines do not recommend or indicate caution when associating NOACs with: strong inhibitors of both cytochrome P450 3A4 (CYP3A4), permeability glycoprotein (P-gp) [43,44], strong inducers of P-gp and/or CYP3A4 (such as rifampicin, carbamazepine etc.) [43,44].

Other anticoagulants, platelet inhibitors (e.g., aspirin, clopidogrel, ticlopidine, prasugrel, ticagrelor, others), non-steroidal anti-inflammatory drugs increase the risk of bleeding. Therefore, such combinations should be carefully balanced [43,44].

8. The assessment of kidney function is recommended in all AF patients to detect kidney disease and correct the dose (Class I, level A) [43,44].

9. All AF patients treated with oral anticoagulation should be considered for at least yearly renal function evaluation to detect chronic kidney disease (Class IIa, level B) [43,44].

SPECIFIC RECOMMENDATIONS FOR PATIENTS WITH RENAL IMPAIRMENT

Mild to moderate CKD: all four NOACs seem to be safe. Dabigatran 110 mg/daily is recommended in patients with CrCl < 50 ml/min at high risk of bleeding [44].

Severe CKD: CrCl of 15-29 ml/min: there are no randomized clinical trials data on the use of NOACs for stroke prevention in AF patients with severe CKD or on renal replacement therapy [44].

Doses of Apixaban and Edoxaban must be reduced by 50% and Rivaroxaban by 25% in patients with CKD (stage IV, CrCl of 15-29 ml/min) [44].

CrCl ≤ 15 ml/min and on dialysis: Dabigatran, Rivaroxaban, Apixaban, and Edoxaban are not recommended. Studies with NOACs in patients with end-stage renal dysfunction and on dialysis are ongoing [44].

Dabigatran is primarily cleared by kidneys and should not be the NOAC of the first choice in patients with known CKD, especially stage III or higher [44].

CrCl of >95 ml/min: the studies observed a possibly decreased efficacy of Edoxaban 60 mg OD compared with Warfarin was observed; post hoc analyses revealed a similar effect also for Rivaroxaban and Apixaban [44].

After kidney transplantation: there are no data on the use of NOACs

DOSING NOACS IN FEMALES WITH CKD

Dabigatran 110 mg BID: in patients with CrCl< 50 ml/min at high risk of bleeding.

Rivaroxaban low doses: 15 mg, Apixaban: 2.5 mg BID or Edoxaban: 30 mg OD (or reduction to 15 mg QD), are approved in Europe for patients with severe CKD (stage IV, CrCl of 15-29 ml/min) [43,44].

In patients on NOACs, renal function has to be monitored every year.

If renal function is impaired (CrCl ≤ 60 ml/min), six monthly checks are required.

Monitoring scheme for renal impairment detection:

(i) CrCl ≥60 ml/min (CKD stage I and II) -monitor every year

(ii) CrCl 30–60 ml/min (CKD stage III) - monitor every six months in older women (>75 years) or frail patients on Dabigatran

(iii) CrCl ≤30 ml/min (CKD stage IV) - monitor every three months

Acute illness often transiently affects renal function (infections, acute heart failure), and therefore should trigger re-evaluation [43,44].

Specific recommendations for patients with hepatic impairment: treatment initiation and follow-up necessitate a specialized center and a multidisciplinary team (including a hepatologist and a hematologist) [44]; in AF patients with Child B liver cirrhosis, Rivaroxaban should not be used. Dabigatran, Apixaban and Edoxaban will be used with caution [44]; NOACS are contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk [44].

CONCLUSIONS

Females with AF are at increased risk of stroke compare to males.

The phase III clinical studies with Dabigatran, Rivaroxaban, Apixaban, and Edoxaban in women with AF showed that these drugs provide significant reductions in the rate of stroke or systemic embolism, hemorrhagic stroke, all-cause mortality, and intracranial hemorrhage compared with Warfarin. The relative efficacy and safety are consistent across many women with AF, including the elderly and those with moderate and mild renal impairment. NOACs have important benefits in safety and bleeding compared with VKA treatment.

There are insufficient data to support higher susceptibility of bleeding with NOACs therapy in women than men, and this assumption necessitates further trials. Guidelines do not recommend a specific NOAC based on patient gender alone. Drug selection should take into consideration individual characteristics.

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