Published in final edited form as:

Med Clin North Am. 2015 March ; 99(2): 417–430. doi:10.1016/j.mcna.2014.11.012.

Anti-Thrombotic Management of Atrial Fibrillation in the Elderly

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SYNOPSIS

Compared to younger patients, older patients with atrial fibrillation (AF) have an increased risk of stroke and systemic embolism^{1, 2}. For the majority of patients, oral anticoagulation (OAC) remains the most effective way to reduce this risk. While vitamin K antagonists (VKAs) have been used for decades, the more recent development of non-vitamin K dependent oral anticoagulants (NOACs) provides clinicians with broader selection of anticoagulants for stroke prevention in older AF patients. In this review, we discuss stroke risk-stratification tools for clinical decision making, review pharmacologic options for the prevention of stroke, and highlight several practical considerations to the use of these agents in older adults.

Keywords

Anticoagulation; Atrial Fibrillation; Elderly; Bleeding; Warfarin; Antiplatelet Agents; Risk Stratification

INTRODUCTION

OAC is the most effective way to prevent thromboembolic disease in patients with AF¹. For decades, aspirin and VKAs were the primary agents used to prevent thromboembolic disease in patients with AF. The approval of NOACs has now expanded the range of therapeutic agents available to providers. Nevertheless, the safe and effective use of NOACs in older adults remains less well established and understood, despite the marked increase in the prevalence of both AF and AF-associated thromboembolism in this population^{1–4}. In this review, we discuss strategies to assess bleeding and thrombosis risk in older adults with AF and summarize pharmacologic options for the prevention of stroke, TIA, and systemic embolism. We will highlight practical considerations to the selection and use of these agents in older adults to aid clinical decision making.

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MANAGEMENT GOALS

The aim of OAC is to prevent the devastating consequences of stroke in older adults with AF while minimizing complications from treatment. Older patients are at increased risk of bleeding complications, adding to the complexity of their treatment. The decision to use antithrombotic therapy in an individual patient with AF requires an estimate of the baseline stroke risk without treatment and the risk of bleeding (especially intracranial hemorrhage - ICH) with treatment, followed by determination of the patient's values and preferences through shared decision-making. Periodic re-evaluation of the patient's stroke and bleeding risk is essential¹. Unfortunately, there are still important limitations to accomplishing these goals.

Stroke Risk Assessment

Stroke risk in individual AF patients varies from less than 1% per year to more than 18% per year and depends on the presence, number, and relative predictive strength of different clinical risk factors for stroke, and not on whether AF is paroxysmal, persistent, or permanent. The strongest risk factors are the presence of mechanical heart valves or mitral stenosis, and these patients all require OAC¹. For patients with nonvalvular AF, the four strongest stroke predictors are prior stroke and/or TIA (RR=2.5), hypertension (RR=2.0), diabetes mellitus (RR=1.7), and age (RR=1.5 per decade)².

These clinical risk factors have been variably combined into different stroke risk stratification tools, including the CHADS₂ and CHA₂DS₂-VASc (Tables 1 & 2)^{5, 6}. The CHA₂DS₂-VASc adds female sex, vascular disease and age 65–74 to the risk factors included in the CHADS₂ score. A systematic review of validation studies concluded that these two tools have the best – albeit modest – discrimination ability for stroke (c-statistics of 0.71 and 0.70, respectively)⁷. Current clinical practice guidelines recommend the use of CHA₂DS₂-VASc over CHADS₂ due to several advantages^{1, 8–10}. Older age (> 75 years) is the single most important risk factor for stroke (4.0–5.0%/yr, HR 3.0–3.5), greater than hypertension, diabetes, or heart failure, thereby warranting extra weight (2 points) as a risk factor^{11, 12}. While the two scores provide similar identification of AF patients at high stroke risk, use of CHA₂DS₂-VASc improves stratification of patients considered “low” (score=0) and “intermediate” (score=1) risk by CHADS₂^{11, 13}. CHA₂DS₂-VASc identifies up to 22% of AF patients with a CHADS₂ score of 0 whose annual event rate may not be low (0.84% for CHA₂DS₂-VASc score=0 to 3.2% for CHA₂DS₂-VASc score=3), and may benefit from OAC^{11, 13}. Thus, CHA₂DS₂-VASc better identifies the “truly low risk” cohort whose annual event rate is <1%, and in whom anticoagulation can be safely deferred^{11, 14, 15}.

Current guidelines for antithrombotic therapy in non-valvular AF vary in their recommendations (Table 3)^{1, 8–10}. For a CHA₂DS₂-VASc score of 0, no antithrombotic therapy (including no aspirin) is recommended. For a score of ≥ 2, all recommend some form of OAC, with NOACs generally preferred over warfarin. However, there is no consensus on OAC for patients with a CHA₂DS₂-VASc score of 1. The 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines (AHA/ACC/HRS-2014) suggest that clinicians “consider” the options of no antithrombotic therapy versus OAC versus aspirin for these patients¹. In contrast, the 2014 National

Institute for Health and Care Excellence (NICE)¹⁰, the 2012 Canadian Cardiovascular Society (CCS)⁸, and the 2012 European Society of Cardiology (ESC)⁹ guidelines recognize that women with AF < 65 years with no other stroke risk factors are at very low risk of stroke and should not receive any antithrombotic therapy^{16, 17}. The NICE guideline states that OAC be “considered” for men with a CHA₂DS₂-VASc score of 1 while the ESC “recommends” OAC for them. Because AF patients age 65–74 years with no other stroke risk factors have annual stroke rates of about 2% per year¹², the CCS “recommends” OAC for them but not for patients whose only risk factor by CHA₂DS₂-VASc is female sex or vascular disease.

Bleeding Risk Assessment

An AF patient’s risk of fatal or disabling bleeding must be assessed when making decisions about antithrombotic therapy. A recent systematic review concluded that the HAS-BLED score (Tables 4 & 5) provides the best, although modest (c-statistic 0.58–0.80), estimation of major bleeding risk for warfarin OAC in AF patients^{7, 18}. However, the HAS-BLED and other bleeding risk scores have important limitations. At least 80% of major bleeds predicted by these tools are extracranial hemorrhages (especially gastrointestinal) that carry low rates of mortality (<5–6%) and rare disability¹⁹. Of much greater concern are ICHs, which constitute 15–20% of major bleeds during warfarin treatment and are responsible for 90% of fatal bleeds¹⁹. ICH carries rates of mortality and severe disability of 46% and 22%, respectively, in AF patients treated with warfarin²⁰.

None of the bleeding risk scores can quantitatively estimate absolute ICH risk, nor can these scores identify AF patients in whom the risk of ICH plus fatal or disabling extracranial hemorrhage is likely to exceed the risk of fatal or disabling ischemic stroke. Additionally, these bleeding risk scores have been validated for warfarin OAC but not yet for NOACs. One recent guideline suggests that current bleeding risk scores do not have sufficient clinical utility to recommend their use¹. Most current recommendations suggest that the HAS-BLED score not be used to exclude patients from OAC, but rather to systematically identify and then eliminate modifiable bleeding risk factors such as uncontrolled hypertension, inadequate warfarin anticoagulation with labile INRs, unnecessary concomitant use of aspirin or NSAIDs, and excessive alcohol use^{8–10}.

PHARMACOLOGIC STRATEGIES

The elderly present a unique challenge in antithrombotic management, due to the frequency of associated co-morbidities that increase the risk of both stroke and bleeding, multiple drug therapy, concerns about compliance and cognitive impairment, low body weight, increased risk of falls, and decreased renal clearance of medications.

Oral Anticoagulation with Warfarin

Underutilization—Compared to no treatment, warfarin decreases the risk of stroke by approximately 2/3 and death by 1/4, with an average number needed to treat (NNT) for 1 year to prevent 1 stroke of 37²¹. Despite compelling evidence of the benefits of warfarin on stroke prevention, it remains underutilized, with estimates that less than 1/2 of eligible AF

patients without contraindications are receiving treatment^{22, 23}. The challenges with warfarin are well-known and include unpredictable pharmacodynamics and pharmacokinetics, narrow therapeutic window, and numerous drug-drug and food-drug interactions, which necessitate frequent laboratory monitoring and dose adjustments.

Also contributing to suboptimal warfarin utilization are patient and physician fears of bleeding. Physicians are less likely to anticoagulate older patients, even in the absence of contraindications, due to the perception that the risks of treatment outweigh the benefits^{23, 24}. Each advancing decade of life is associated with a 14% reduction in warfarin use, independent of other risk factors for stroke³. Additionally, patients frequently refuse anticoagulation. For example, 1/3 of patients enrolled in the AVERROES and ACTIVE A studies refused a VKA, due to the associated inconvenience and perceived bleeding risk^{25, 26}.

Fear of Falls—Clinicians may disproportionately consider the risk of traumatic ICH from falls in their assessment of the net clinical benefit of OAC for older AF patients. Clinician perception of fall risk is a key determinant in their decision to use OAC²⁴. However, studies of AF patients on OAC and who are at high fall risk do not consistently demonstrate an increased risk of traumatic ICH²⁷. A modeling study suggested that AF patients at higher risk of stroke would have to fall > 295 times/year before the risk of traumatic ICH would exceed the risk of ischemic stroke; yet, in older persons who fall, the mean number of falls is only 1.8/year^{28, 29}. In older Medicare beneficiaries with traumatic brain injury on OAC, resumption of warfarin therapy following hospital discharge resulted in a 17% reduction in the combined outcome of ischemic and hemorrhagic stroke³⁰. Based on these data, many investigators propose that high fall risk is not a reason to avoid OAC^{10, 27, 28}. For clinicians with significant concerns about individual patients, a referral to a faint and fall clinic or a comprehensive fall risk assessment can be considered.

Net clinical benefit of warfarin—Based on the need to balance the risks of ischemic thromboembolism (TE) with the risks of fatal and disabling major bleeding, prospective cohort studies of AF patients have assessed the “net clinical benefit” of warfarin. This has been established as the annual rate of ischemic strokes prevented by warfarin minus the annual rate of ICH caused by warfarin, the latter multiplied by a factor of 1.5 to reflect the greater clinical severity of ICH than ischemic stroke^{16, 31, 32}. Overall, the impact of warfarin is much higher on TE risk than on ICH risk³¹. Due to increasing risk for stroke with aging and a relatively constant increase in ICH risk with aging, the net clinical benefit of warfarin improves progressively with advancing age and is greatest for AF patients > 85³¹. Net clinical benefit of warfarin also improves progressively with major bleeding risk as measured by the HAS-BLED score; that is, warfarin OAC decreases ischemic stroke rate more than it increases ICH rate at all levels of bleeding risk^{16, 32}. Moreover the net clinical benefit of warfarin is favorable in all groups except with CHA₂DS₂-VASc score of 0, confirming their “truly low risk” status^{16, 32}. In this large study, only 0.4% of patients had a bleeding risk exceeding their stroke risk¹⁶. Thus, in almost all AF patients, particularly the elderly and those at high bleeding risk, the risk of ischemic stroke without OAC exceeds the risk of intracranial bleeding with OAC.

Reflective of this data, the pendulum in antithrombotic management is swinging away from a focus on identifying high-risk patients for treatment with OAC, and towards identification of the “truly low risk” patient, in whom OAC can safely be deferred, while considering all other patients for anticoagulation treatment. Use of the CHA₂DS₂-VASc scoring system can help in identifying this subgroup of patients.

Antiplatelet Therapy

Aspirin monotherapy—In some settings, aspirin has been historically considered a safer alternative to OAC²⁴. Aspirin was previously recommended for stroke prevention in patients considered low-risk for stroke, and seen as an acceptable alternative to OAC for patients at intermediate risk of stroke and for those who were deemed unsuitable for, or choose not to take warfarin³³. There is moderate evidence from numerous RCTs that aspirin decreases the risk of nonfatal stroke by 21% compared to no therapy, but at a cost of a 50–60% increase in major extracranial bleeding^{21, 34}. However, in comparison to aspirin monotherapy, warfarin is superior, with a 37% greater reduction in strokes²¹. The relative risk of ICH is doubled with warfarin compared to aspirin, but this represents only a small absolute increase (0.2–0.4%/year)²¹.

Efficacy data for aspirin use in the elderly is even less compelling. In the BAFTA trial, patients aged ≥75 years were randomized to either warfarin or aspirin 75mg daily. Warfarin was associated with a significant reduction in fatal or disabling stroke, ICH, or systemic embolus (1.8 vs 3.8%/year; RR 0.48, NNT 50), with a similar risk of major hemorrhage³⁵. The yearly risk of a major bleed on aspirin was not insignificant, at 2% per year³⁵. Other studies have also demonstrated higher rates of side-effects and intolerance to aspirin than warfarin³⁶.

In a net clinical benefit analysis, aspirin was not found to be protective of thromboembolism, with an increased bleeding risk compared to no treatment, and a similar bleeding risk to warfarin, leading the authors to suggest that aspirin should not be used for any patient with AF³². Aspirin is significantly less effective at stroke prevention than warfarin in older patients, with no difference in major bleeding^{4, 35}. Additionally, the relative benefit of antiplatelet therapy has been shown to decrease significantly with age, but the relative benefit of warfarin does not⁴. Since stroke risk increases with age, the absolute benefit of OAC over antiplatelet therapy continues to increase as patients age⁴. Reflective of this, some guidelines no longer recommend use of aspirin as an acceptable alternative to OAC^{9, 10, 34}.

Dual antiplatelet therapy—Compared to aspirin monotherapy, dual antiplatelet therapy offers superior stroke prevention (2.4 vs 3.3%/yr, RR 0.72), albeit at the expense of increased major bleeding (2.0 vs 1.3%/yr, RR 1.57) and ICH (0.4 vs 0.2%/yr, RR 1.87)²⁵. The ACTIVE W trial evaluated dual antiplatelet therapy as a potential alternative to warfarin in AF patients at high risk of stroke³⁷. This trial was stopped early as warfarin significantly reduced the risk of stroke by 42% compared to aspirin plus clopidogrel (3.93 vs 5.60%/yr, NNT 100), with no difference in mortality or major bleeding. Similar data was seen when apixaban was compared to the combination of aspirin and clopidogrel in the AVERROES

trial, which was terminated prematurely due to a 50% reduction in stroke rate with apixaban, without any differences in bleeding. Apixaban was also associated with fewer adverse events and a lower rate of discontinuation²⁶.

For patients who refuse OAC or are deemed unsuitable candidates for reasons other than bleeding risk, the combination of aspirin and clopidogrel should be considered, and this is now recommended in some guidelines over aspirin monotherapy^{9, 34}. Patients should be counseled that this regimen offers inferior stroke prevention compared to OAC, with no difference in bleeding risk.

Non-vitamin K dependent oral anticoagulants (NOACs)

Recently, the FDA has approved three NOACs (dabigatran, rivaroxaban and apixaban) for use in AF, with an additional agent (edoxaban) expected to be available in the near future (Table 6). These newer drugs provide clinicians with additional therapeutic options to prevent stroke in AF, and lack many of the limitations inherent to warfarin. They have predictable pharmacodynamic and pharmacokinetic profiles, a wide therapeutic window, shorter half-life with rapid onset/offset of action, less drug-drug interactions, few to no food-drug interactions, no need for routine laboratory monitoring, and fixed dosing schedules.

Dabigatran is an oral direct thrombin inhibitor, while rivaroxaban, apixaban and edoxaban are Factor Xa inhibitors. Each of these drugs are either non-inferior or superior to warfarin for stroke prevention, with markedly less intracranial bleeding (Table 7)^{38–41}. Dabigatran, rivaroxaban, and edoxaban caused higher rates of GI bleeding than warfarin. To better define the efficacy and safety of these medications in subgroups, meta-analyses of these phase 3 clinical trials have been performed^{42, 43}. NOACs are associated with an approximately 12% decrease in mortality compared to warfarin, a 20% decrease in stroke or systemic embolus, and most impressively, a 50% reduction in ICH. The net clinical benefit of NOACs is not yet as clearly established as it is for warfarin. However, due to their 50% lower risk of ICH, modeling analyses suggest that NOACs may provide even greater net clinical benefit than warfarin for AF patients with a CHA₂DS₂-VASc score ≥ 1 ⁴⁴.

Efficacy and Safety of NOACs in Older Patients—Although there are no RCTs that have enrolled exclusively older patients with AF, the available evidence suggests that the safety and efficacy of NOACs in older adults is similar to the overall study population⁴⁵. A recent meta-analysis of randomized trials of NOACs in patients ≥ 75 years showed significantly lower rates of stroke and systemic embolus compared to conventional treatment, with no increased risk of bleeding⁴⁶. In the ROCKET AF trial, the risk of any major bleeding was similar among patients who received rivaroxaban or warfarin, regardless of age, but intracranial bleeding was lower with rivaroxaban^{39, 47}. In ARISTOTLE, the overall risk of stroke, death, and major bleeding increased with aging, but apixaban was more effective than warfarin in reducing these outcomes, irrespective of age^{40, 48}. Due to increasing risk of stroke as patients age, the absolute benefit of NOACs over warfarin was greatest in the elderly. In contrast to rivaroxaban and apixaban, in the RE-LY trial, there was a highly significant interaction between treatment and age for major bleeding. In patients < 75 , both doses of dabigatran were associated with a lower risk of major bleeding compared

to warfarin. However, patients ≥ 75 years experienced similar rates of major extracranial bleeding compared to warfarin with dabigatran at a dose of 110 mg twice daily, but a trend toward higher risk of extracranial bleeding with the 150 mg twice daily. ICH was reduced with both doses of dabigatran compared to warfarin, regardless of age^{38, 49}. These data suggest that the safety of Xa inhibitors is less dependent on age than is dabigatran, with one possible explanation being that they are less dependent on renal clearance than dabigatran⁴⁸.

Disadvantages of NOACS—The potential disadvantages associated with the NOACs include twice daily dosing regimen (with the exception of rivaroxaban), short duration of action, lack of a reliable and readily available monitoring option, and lack of antidote (Table 8). Discussion of potential laboratory monitoring and reversal agents is beyond the scope of this article. We have chosen to focus on renal impairment, since renal function declines with advancing age and patients with severe renal impairment ($\text{CrCl} < 30 \text{ mL/min}$, $< 25 \text{ mL/min}$ for apixaban) were excluded from the clinical trials.

NOACs in older patients with renal impairment—NOACs have not yet been robustly studied in patients with severe renal impairment and are not recommended in patients with end-stage renal disease or on hemodialysis. The incidence of renal impairment increases with age, and renal impairment increases the risk of both thromboembolism and bleeding complications in patients with AF, independent of other risk factors^{49, 50}. Since AF is primarily a disease of the elderly, these two conditions often coexist, leading to significant concerns about bleeding risk. In RE-LY, patients on either dabigatran or warfarin with a $\text{CrCl} < 50 \text{ mL/min}$ experienced a 2-fold higher risk of major bleeding, compared to those who had a $\text{CrCl} \geq 80 \text{ mL/min}$ ⁴⁹. In ROCKET-AF, reduced dose rivaroxaban in patients with $\text{CrCl} 30\text{--}49 \text{ mL/min}$ preserved the benefit over warfarin without increasing bleeding and with fewer fatal bleeds⁵¹. In ARISTOTLE, apixaban reduced the rate of stroke, death and major bleeding compared to warfarin regardless of renal function, including in patients > 75 ^{48, 50}. Thus, all three trials showed higher rates of bleeding and stroke with impaired renal function regardless of randomized treatment assignment, suggesting no increased risk with NOACs as compared to warfarin.

Although NOACs appear to be at least as safe as warfarin in the short-term and reduce the risk of intracranial bleeding, longer-term data is still needed. There may also be subtle differences between the NOACs in rates of ischemic stroke, MI, bleeding and death, but the lack of head-to-head trials makes this difficult to discern. Nevertheless, when considered overall, the significant decrease in ICH, fixed dosing schedules, lack of routine laboratory monitoring, and fewer drug-drug interactions make the NOACs an alternative to warfarin for some older patients (Table 8).

Future Considerations and Summary

In summary, age remains one of the strongest risk factors for stroke in patients with AF. The use of guideline-recommended stroke scoring systems, in combination with a bleeding risk factor assessment can help guide providers in determining the net clinical benefit of antithrombotic therapy in older adults with AF. Recently approved NOACs may offer select

advantages for the prevention of stroke and systemic embolism in older patients with AF. Future studies may further elucidate the net clinical benefit of NOACs in the elderly and help guide more individualized AC selection and management.

Acknowledgments

This work was supported by the National Institutes of Health and the National Institute of Aging (HL092161, AG040631, HL112311, and AG048022) and the University of Utah Center on Aging. We thank Dr. Barry Stults for his valuable comments and expert suggestions.

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KEY POINTS

- Older age remains one of the strongest risk factors for stroke in patients with atrial fibrillation (AF)
- Validated stroke risk stratification schemes, such as the CHADS₂ and CHA₂DS₂-VASc, should be used to estimate stroke risk and guide anticoagulation decisions in older adults with AF
- Bleeding risk scores, such as HAS-BLED, should not be used to exclude patients from oral anticoagulation (OAC), but rather to identify modifiable bleeding risk factors that can be managed to reduce a patient's risk of bleeding from anticoagulation
- The significant decrease in intracranial bleeding risk with non-vitamin K OACs (NOACs), combined with their fixed dosing schedules and fewer drug-drug interactions, provide potential advantages over VKAs in older patients with AF
- Antiplatelet agents should be reserved primarily for patients who are deemed unsuitable for, or refuse, OAC

Table 1
CHADS₂ and CHA₂DS₂-VASc Risk Stratification Score for Stroke Risk Assessment in AF

CHADS ₂				CHA ₂ DS ₂ -VASc			
Risk Factor		Score	Risk Factor		Score	Score	
C	Congestive heart failure	1	C	Congestive heart failure	1	1	1
H	Hypertension (>140/90)	1	H	Hypertension	1	1	1
A	Age 75	1	A	Age 75	1	2	2
D	Diabetes mellitus	1	D	Diabetes	1	1	1
S	Stroke/Transient ischemic attack/Thromboembolism	2	S	Stroke/Transient ischemic attack/Thromboembolism	2	2	2
			V	Vascular disease (prior myocardial infarction, peripheral arterial disease, or aortic plaque)	1	1	1
			A	Age 65–74	1	1	1
			Sc	Sex category (female sex)	1	1	1
Maximum Score		6				9	9

Table 2

Comparison of Thromboembolic Event Rate by CHA₂DS₂-VASc Score per 100 Person Years in Three Prospective Real World Population Cohorts

CHA ₂ DS ₂ -VASc Score	Friberg ¹⁴	Singer ¹⁵	Olesen ¹¹ 1 yr follow-up
0	0.3	0.04	0.78
1	0.9	0.55	2.01
2	2.9	0.83	3.71
3	4.6	1.66	5.92
4	6.7	2.80	9.27
5	10.0	4.31	15.26
6	13.6	4.77	19.74
7	15.7	4.82	21.50
8	15.2	7.82	22.38
9	17.4	16.62	23.64

Data from Refs 11,14,15

Table 3

Antithrombotic Therapy Recommendations For Non-Valvular Atrial Fibrillation.

CHA ₂ DS ₂ -VASc Score	AHA/ACC/HRS 2014 ¹	NICE 2014 ⁸	CCS 2012 ⁸	ESC 2012 ⁷
0	No Rx	No Rx	No Rx	No Rx
1	OAC <u>or</u> ASA <u>or</u> No Rx	Female sex: No Rx Male sex: Consider OAC	Age 65y: NOAC preferred over VKA Vascular disease or female sex: ASA is a reasonable alternative	Female sex: No Rx Age 65 <u>or</u> vascular disease: NOAC VKA with TTR>70% as an alternative to NOAC ASA only for patients who refuse <u>or</u> cannot tolerate OAC
2	OAC with Warfarin, Dabigatran, Rivaroxaban, <u>or</u> Apixaban	OAC with NOAC or VKA	OAC with NOAC preferred to VKA	OAC with NOAC VKA with TTR>70% as an alternative to NOAC

Data from Refs 1,7,8

Table 4

The HAS-BLED Bleeding Risk Score.

	Risk Factors	Score
H	Hypertension ^a	1
A	Abnormal liver ^b or kidney function ^c	1 or 2
S	Stroke	1
B	Bleeding ^d	1
L	Labile INR ^e	1
E	Elderly ^f	1
D	Drugs ^g or alcohol ^h	1 or 2

^a >160mmHg systolic

^b cirrhosis, bilirubin >2xULN (upper limit of normal), Aspartate aminotransferase/Alanine aminotransferase/Alkaline phosphatase>3xULN

^c renal dialysis, history of renal transplant or serum creatinine ≥ 2.26 mg/dL

^d requiring hospitalization, decrease in Hemoglobin > 2 g/L or requiring blood transfusion

^e Time in Therapeutic Range < 60%

^f age >65 years

^g Use of antiplatelet agents or non-steroidal anti-inflammatory drugs

^h >8 drinks per week

Table 5

Major Bleeding Rates Based on the HAS-BLED Risk Category.

Score	Risk Category	Bleeds/100 patient years
0–1	Low	1.2 – 2.8
2	Moderate	3.6 – 5.4
3	High	6.0–9.5

Table 6

Comparison of NOACs for the Prevention of Stroke and Systemic Embolism in AF.

	Rivaroxaban	Dabigatran	Edoxaban	Apixaban
Pro-Drug or Drug	Drug	Pro-Drug	Drug	Drug
Target	Factor Xa	Thrombin	Factor Xa	Factor Xa
Mean half-life (t_{1/2})	7–11 hours	12–17 hours	9–11 hours	8–15 hours
T_{max}	2–4 hours	0.5–2 hours	1–2 hours	3–4 hours
Protein binding	93%	35%	55%	87%
Dosing Regimen *	20 mg Daily	150 mg BID	Daily	5 mg BID
Dose adjustments	15 mg Daily if CrCl 15–50	75 mg BID if CrCl 15 to 30	N/A	2.5 mg BID if 2 of the following: Age ≥ 80 years, weight ≥ 60 kg, or serum creatinine ≤ 1.5 mg/dL
Major interactions	P-gp, CYP3A4	P-gp	P-gp	P-gp, CYP3A4
Estimated renal excretion	66%	80%	35%	25%
Food Effect	Delayed absorption	Delayed absorption	None	None

* FDA-approved dosing, BID, twice daily

Table 7

Summary of Key, Randomized Clinical Trials Comparing NOACs to a VKA for the Prevention of Stroke and Systemic Embolism in AF.

	Rivaroxaban	Dabigatran	Edoxaban	Apixaban
Phase III RCT	ROCKET AF	RE-LY	TIMI 48-ENGAGE	ARISTOTLE
Population	NVAF and 2 RF*	NVAF and 1 RF*	NVAF and CHADS ₂ 2	NVAF and 1 RF*
Patients, n	14,264	18,113	21,105	18,201
Study Design	double-blind, double-dummy	PROBE	double-blind, double-dummy	double-blind, double-dummy
Primary Objective	Non-Inferior Efficacy	Non-Inferior Efficacy	Non-Inferior Efficacy	Non-Inferior Efficacy
Study drug dose(s)	20mg daily	110mg or 150mg BID	60mg daily	5mg BID
Renal dose	15mg daily	None	30mg daily ^a	2.5mg BID
Age, y	73.0	71.5	72.0	70.0
Male Gender, %	60.3	63.6	61.9	64.7
CHADS₂ Score	3.5	2.1	2.8	2.1
TTR, %	55	64	65	62
Aspirin Use, %	36.5	39.8	29.3	30.9

* risk factors (RF): age ≥ 75 y; history of stroke, transient ischemic attack, or systemic embolism; symptomatic heart failure and/or left-ventricular ejection fraction <40%; diabetes mellitus; and/or need for antihypertensive treatment.

^a For patients with a CrCl 30–50 mL/min, a weight ≥ 60kg, or the concomitant use of verapamil, quinidine, or dronedarone

PROBE: prospective open-label blinded endpoint evaluation

Table 8

Considerations when Choosing Between a VKA or a NOAC for Older Patients with AF.

Consideration or Factor	Potentially Preferred OAC	Comment
Severe Renal Impairment (e.g. CrCl 15–30 mL/min)	VKA, Reduced Dose Dabigatran 75mg BID, or Reduced Dose Rivaroxaban 15mg Daily	VKA elimination is independent of any renal impairment
End-Stage Kidney Disease	VKA	VKA elimination is independent of any renal impairment
History of ICH	Dabigatran, Rivaroxaban, Apixaban, Edoxaban	All NOACs reduced the risk of ICH compared to VKA
Mechanical Heart Valves	VKA	NOACs only approved in NVAf
Unstable INR or Inability to Comply with Regular INR Monitoring	Dabigatran, Rivaroxaban, Apixaban, Edoxaban	Predictable Pharmacokinetics without Need for Routine Monitoring
Poor Adherence to Taking Medication	VKA	Longer Half-Life, Ability to Monitor Compliance with INR
Concomitant Use of Azole Antimycotics or Ritonavir	Dabigatran, VKA	Azole Antimycotics or Ritonavir Increase Blood Concentration of FXa Inhibitors
Dyspepsia	VKA, Rivaroxaban, Apixaban, Edoxaban	High Incidence of Dyspepsia with Dabigatran
Poor Compliance with Twice Daily Medication	VKA, Rivaroxaban	Once Daily Dosing Regimen
History of GI Bleeding	VKA, Apixaban	Higher Rates of GI Bleeding with Dabigatran, Rivaroxaban, and Edoxaban
Cost Concerns	VKA	NOACs may be Cost Prohibitive to Some Patients