Individualized approaches to thromboprophylaxis in atrial fibrillation

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Atrial fibrillation (AF) is the most common arrhythmia worldwide. The prevalence of AF in persons older than 55 years is at least 33.5 million globally and is predicted to more than double in the next half-century. Anticoagulation, heart rate control, and heart rhythm control comprise the 3 main treatment strategies in AF.

Anticoagulation is aimed at preventing debilitating stroke, systemic embolism, and associated mortality. Historically, anticoagulation in AF was achieved with a vitamin K antagonist such as warfarin, which is supported by evidence demonstrating reduced incident stroke and all-cause mortality. However, warfarin has unpredictable pharmacokinetics with many drug-drug interactions that require regular monitoring to ensure patients remain in the therapeutic anticoagulant range. Non–vitamin K antagonist oral anticoagulants including dabigatran, rivaroxaban, apixaban, and edoxaban provide a possible solution to these issues with their more predictable pharmacokinetics, rapid onset of action, and greater specificity. Results from large randomized, controlled trials indicate that these agents are at least noninferior to warfarin in prevention of stroke. These trials also demonstrate a consistently lower incidence of intracranial hemorrhage, almost always all life-threatening bleeds, and many forms of major bleeds with the possible exception of gastrointestinal and some other forms of mucosal bleeding, compared with warfarin.

Patients with AF are a heterogeneous population with diverse risk of stroke and bleeding, and different subgroups respond differently to anticoagulation. Important clinical questions have arisen regarding optimal anticoagulation drug selection in distinct populations such as those with renal impairment, older age, coronary artery disease, and heart failure as well as those at particularly high risk for bleeding or thromboembolism. In this review, treatment strategies in AF management are discussed in the context of different individual subgroups of patients. (Am Heart J 2016;173:143-58.)

Atrial fibrillation (AF) is the most common arrhythmia, affecting 1% to 2% of the population in North America and Europe.[1] Atrial stasis, endothelial dysfunction, and increased coagulability lead to thrombus formation resulting in a 4- to 5-fold increased risk of ischemic stroke relative to the nonaffected population.[2] Atrial fibrillation is responsible for at least 15% of all strokes, rising to 25% in the elderly (≥70 years).[3,4] Strokes resulting from AF are more severe than those of other etiology, with a higher mortality and greater functional deficit.[5]

The last few years has seen a dramatic increase in the options available for AF thromboprophylaxis. Aspirin, once widely used, is inferior to warfarin and is not significantly better than placebo in stroke prevention.[6–8] The National Institute for Health and Care Excellence (NICE) along with the European Society of Cardiology (ESC) guidelines no longer recommend antiplatelet therapy unless a patient refuses anticoagulation[9,10] (Table I). Well-controlled warfarin therapy is extremely effective in reducing the risk of ischemic stroke (relative risk [RR] reduction of 64%).[11] Achieving good control requires careful monitoring, with regular dose adjustments to remain within a target international normalized ratio (INR) range. This is complicated by genetic variation involved in warfarin metabolism, slow onset of action, and complex pharmacology with many drug-drug and dietary interactions.

Unlike warfarin, the non–vitamin K antagonist oral anticoagulants (NOACs) have more predictable pharmacokinetic profiles, wide therapeutic windows, and minimal drug-drug interactions and do not require regular therapeutic monitoring. NOACs are at least equal in efficacy to warfarin for stroke prevention in AF; however, each agent exhibits a unique set of clinical properties that may favor their use in particular individuals.[12–16]

Realizing the full potential of recent advances in AF management options will require individualized treatment strategies, incorporating individual patients' views and preferences. In this review, we consider the evidence relating to oral anticoagulation in patients at thromboembolic risk, specifically focusing on distinct subgroups of the AF population.

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Table I. Anticoagulation guidelines in AF

Guideline	CHA_2DS_2-VASc = 0	CHA_2DS_2-VASc = 1	CHA_2DS_2-VASc ≥ 2
AHA/ACC/HRS 2014[17]	Reasonable to omit antithrombotic therapy	Consider aspirin or no antithrombotic therapy	Recommend: dabigatran, rivaroxaban, apixaban, warfarin. In CKD moderate-severe, consider reduced dose dabigatran, rivaroxaban, or apixaban. If CrCl <15 mL/min, prescribe warfarin
ESC 2012[23]	Recommend no antithrombotic therapy	Best option: dabigatran, rivaroxaban, apixaban. Alternative option: adjusted dose VKA (INR 2-3) Female patients <65 y and lone AF: no antithrombotic therapy	Best option: dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, apixaban Alternative option: adjusted dose VKA (INR 2-3) If CrCl <30 mL/min, avoid NOACs
NICE 2014[9]	Do not offer stroke prevention therapy	Men with CHA_2DS_2-VASc = 1: consider anticoagulation including rivaroxaban, dabigatran, apixaban, and VKA; take bleeding risk into account. Female CHA_2DS_2-VASc = 1: do not offer stroke prevention therapy	Offer anticoagulation, including rivaroxaban, dabigatran, apixaban, and VKA. Take bleeding risk into account
CCS 2014[147]	No additional risk factors: no antithrombotic	≥65 y: OAC Prior stroke or TIA; or hypertension; or HF; or diabetes: OAC CAD or vascular disease: ASA NOAC should be used in preference to warfarin in nonvalvular AF	Offer OAC. NOAC should be used in preference to warfarin in nonvalvular AF

Abbreviations: AHA, American Heart Association; ACC, American College of Cardiology; ASA, acetylsalicyclic acid; CCS, Canadian Cardiovascular Society; HRS, Heart Rhythm Society; OAC, oral anticoagulant.

Classification of AF

Atrial fibrillation is not a homogenous arrhythmia and has been classified by presentation and duration of the arrhythmia. The ESC has adopted the following 5 types[10]:

1. First diagnosed with AF
2. Paroxysmal AF
3. Persistent AF
4. Long-standing persistent AF
5. Permanent AF

The American Heart Association/American College of Cardiology/Heart Rhythm Society 2014 guidelines do not recognize first-diagnosed AF as a distinct entity but instead include an additional group named "nonvalvular AF," in whom there is absence of rheumatic mitral stenosis, prosthetic mechanical heart valve, or mitral valve repair.[17] This was supported by the finding that AF increases stroke risk 4- to 5-fold, whereas mitral stenosis or prosthetic heart valve–related AF confers a 20-fold increase in risk compared with patients in sinus rhythm.[2,18] Paroxysmal AF appears to be associated with less thromboembolic events than persistent or permanent AF,[14,16] but regardless, all categories of nonvalvular AF should be managed with the same thromboprophylactic approach based on risk factors and patient preferences irrespective of whether the AF pattern is paroxysmal, persistent, or permanent.[19]

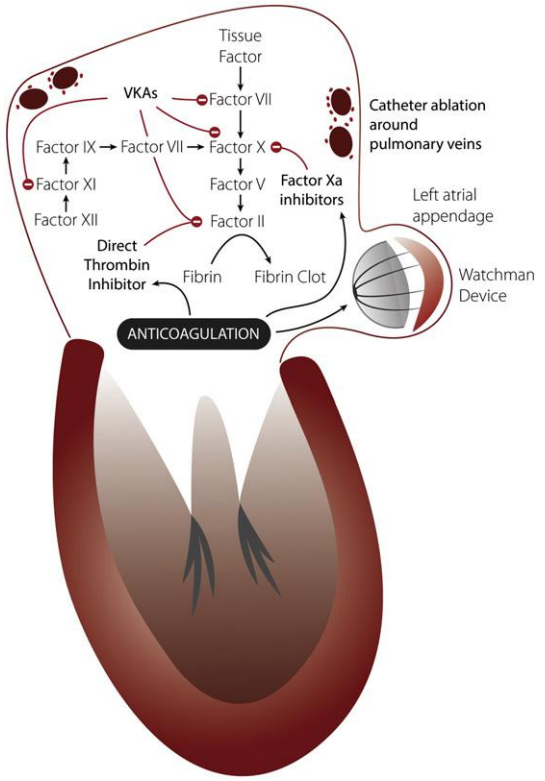
Although helpful to guide prescribing, these categories fail to adequately classify all patients with AF. Remote continuous cardiac monitoring by virtue of cardiac implantable electronic devices has revealed cases of subclinical AF, associated with increased risk of embolic events.[20] A further subgroup of unclassified patients are those with a "pre-AF" status. This population, with a high burden of vascular risk factors, is at significant risk for developing AF. It is unknown whether protection with anticoagulation for near-inevitable atrial tachyarrhythmia provides benefit, but some pilot studies are underway including REVEAL AF[21] and ASSERT-II.[22]

The current AF classification schemes are restricted by simplicity. Many risk factors predict the onset of AF, and a more comprehensive classification system is required that incorporates AF duration and symptoms combined with a risk score for AF onset, persistence, progression, and complications along with markers of atrial remodeling, This model would improve the clinicians' ability to risk stratify their patients and hence guide personalized treatment.[23] This individualized management approach to AF would also benefit from integrating the pathophysiologic type of AF addressing atrial morphology, genetic predisposition, and markers of inflammation and cardiac strain.[24]

Anticoagulation therapies—a multitude of choice

Warfarin is an excellent anticoagulant in AF that reduces stroke by 64% and all-cause mortality by 26%,[8,25] but despite this, physicians underuse it, particularly in elderly patients.[26] This may be partly explained

Figure 1



Mechanism of anticoagulation in AF. Management strategies in AF are focused on the left atrium. Anticoagulation methods target the clotting cascade in the left atrium, where secondary to atrial stasis, fibrin clots readily form. The left atrial appendage is common site for atrial thrombi to form and left atrial occlusion devices, for example, to Watchman Device, help prevent these.

by the properties of warfarin: slow onset, narrow therapeutic range, drug and food interactions,[27] requirement for close monitoring and patient comorbidities. Even when patients are maintained in the therapeutic range of INR (2.0-3.0), there is still the important problem of intracranial hemorrhage (ICH). Reported times in the therapeutic range (TTR) of those on warfarin in trial settings are only 55% to 68% and even this is difficult to replicate everywhere in "real-world" practice.[12–14,16] Although some of these issues with warfarin may be solved by novel vitamin K reductase antagonists such as tecarfarin,[28] over the last 5 years, 4 NOACs have been approved for stroke prophylaxis in patients with nonvalvular AF. NOACs have faster onset than warfarin (time to peak concentration 1-4 vs 96-120 hours), improved side effect profile, and predictable pharmacology, without the impracticalities of regular therapeutic drug monitoring and dose adjustment.[29,30] Currently, 2 classes of NOAC are available[29,31]: direct thrombin inhibitors (dabigatran[12]) and direct factor Xa (FXa) inhibitors (rivaroxaban,[13] apixaban[16] and edoxaban[14]). Large, international, randomized controlled trials (RCTs) have reported all 4 agents to be noninferior, and some superior to warfarin in prophylaxis of ischemic stroke and systemic embolism.[12–14,16] Importantly, each trial must be interpreted in the context of the median TTR achieved in the warfarin arm to avoid artificially increasing or decreasing the perceived benefits of the NOAC and to permit an attempt at indirect comparisons. However, indirect comparison between trials must usually be avoided due to substantial differences in the baseline risk ($CHADS_2$ score; Table II) and dose reduction schedules.

Anticoagulation agents target the coagulation cascade, preventing the synthesis or inhibiting the action of clotting factors.[32] Warfarin prevents the synthesis of vitamin K–dependent coagulation factors, thereby exerting its effects at multiple sites in the coagulation cascade (FII, FVII, FIX, FX, and proteins C, S, and Z).[32] The NOACs are small-molecule, targeted inhibitors of single–clotting factors and therefore have greater specificity on the coagulation cascade (Figure 1).[29]

Direct thrombin inhibitors

Thrombin forms from prothrombin by enzyme cleavage by FXa, which initiates the final common pathway of the coagulation cascade. Thrombin undergoes positive feedback and simultaneously cleaves fibrinogen to fibrin enabling the development of the polymeric protein structure around which the fibrin clot can form. Thrombin is therefore pivotal in the formation of a clot and forms an attractive therapeutic target for anticoagulation.[33]

Dabigatran

Dabigatran was evaluated in the phase III RE-LY (Randomised Evaluation of Long-Term Anticoagulation Therapy) trial. This enrolled 18,113 patients with nonvalvular AF and $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack) >1 (mean 2.1). Patients were randomized to either 110 or 150 mg dabigatran twice daily or to dose-adjusted warfarin (median TTR 64%) over a median follow-up of 2 years. These 2 doses were studied as individual regimens rather than a dosing strategy, A PROBE (Prospective Randomized Open, Blinded Endpoint) design was used.

Dabigatran 150 mg twice daily was superior to warfarin in prevention of stroke or systemic embolism (including ischemic stroke), whereas dabigatran 110 mg twice daily was noninferior to warfarin. Hemorrhagic stroke risk was significantly lower for both regimens compared with warfarin, and major bleeding was significantly lower in patients randomized to 110 mg (RR 0.80, 95% CI 0.69-0.93, P = .003) but not with patients on 150 mg compared with warfarin. Although patients in the 150 mg

Table II. Summary of the clinical trials of the non-VKAs compared with warfarin[23]

	Dabigatran (RE-LY)[12,148]	Rivaroxaban (ROCKET-AF)[13,149–152]	Apixaban (ARISTOTLE)[16,75]	Edoxaban (ENGAGE AF–TIMI 48)[14,153–156]
Drug characteristics				
Mechanism	Direct thrombin inhibitor	FXa inhibitor	FXa inhibitor	FXa inhibitor
Bioavailability (%)	6	70	50	62
Time to peak levels (h)	3	3	3	1.5
Half-life (h)	12-17	5-13	12	10-14
Excretion	80% renal	33% renal, 66% biliary	25% renal, 75% fecal	50% renal, 50% fecal
Study characteristics				
Study design	Randomized, open-label	Randomized, double-blind	Randomized, double-blind	Randomized, double-blind
Patient number	18,113	14,264	18,201	21,105
Follow-up (y)	2.0	1.9	1.8	2.8
Trial arms	Dose adjusted warfarin vs dabigatran 150 mg twice daily, 110 mg twice daily	Dose-adjusted warfarin vs rivaroxaban 20 mg once daily	Dose-adjusted warfarin vs apixaban 5 mg twice daily	Dose-adjusted warfarin vs edoxaban 30 mg once daily, 60 mg once daily
Dose	150 mg twice daily	20 mg once daily	5 mg twice daily	60 mg once daily
Dose in CKD	110 mg twice daily	15 mg once daily (CrCl 30-49 mL/min)	2.5 mg twice daily	30 mg once daily
Baseline patient characteristics				
Age (y)	71.5 ± 8.7 (mean ± SD)	73 (65-78) (median [IQR])	70 (63-76) (median [IQR])	72 (64-78) (median [IQR])
Male sex (%)	63.6	60.3	64.7	61.9
$CHADS_2$ (mean)	2.1	3.5	2.1	2.8

Outcomes (% per year)

	Warfarin (n = 6022), % of pts/y	Dabigatran 150 mg (n = 6076), RR (95% CI)	Dabigatran 110 mg (n = 6015), RR (95% CI)	Warfarin (n = 7133), % of pts/y	Rivaroxaban (n = 7131, RR (95% CI)	Warfarin (n = 9081), % of pts/y	Apixaban (n = 9120), RR (95% CI)	Warfarin (n = 7036), % of pts/y	Edoxaban 60 mg (n = 7035), RR (97.5% CI)	Edoxaban 30 mg (n = 7034), RR (97.5% CI)
Stroke or systemic embolism	1.69	1.11 (0.66, 0.53-0.82)	1.53 (0.91, 0.74-1.11)	2.4	2.1 (0.88, 0.75-1.03)	1.6	1.27 (0.79, 0.66-0.95)	1.5	1.18 (0.79, 0.63-0.99)	1
Ischemic stroke	1.2	0.92 (0.76, 0.60-0.98)	1.34 (1.11, 0.89-1.40)	1.42	1.34 (0.94, 0.75-1.17)	1.05	0.97 (0.92, 0.74-1.13)	1.25	1.25 (1.00, 0.83-1.19)	1.77 (1.41, 1.19-1.67)
Major Bleeding	3.36	3.11 (0.93, 0.81-1.07)	2.71 (0.80, 0.69-0.93)	3.4	3.6 (1.04, 0.90-1.20)	3.09	2.13 (0.69, 0.60-0.80)	3.43	2.75 (0.80, 0.71-0.91)	1.61 (0.47, 0.41-0.55)
Hemorrhagic stroke	0.38	0.10 (0.26, 0.14-0.49)	0.12 (0.31, 0.17-0.56)	0.44	0.26 (0.59, 0.37-0.93)	0.47	0.24 (0.51, 0.35-0.75)	0.47	0.26 (0.54, 0.38-0.77)	0.16 (0.33, 0.22-0.50)
ICH	0.74	0.30 (0.40, 0.27-0.60)	0.23 (0.31, 0.20-0.47)	0.7	0.5 (0.67, 0.47-0.93)	0.80	0.33 (0.42, 0.30-0.58)	0.85	0.39 (0.47, 0.34-0.63)	0.26 (0.30, 0.21-0.43)
All-cause mortality	4.13	3.64 (0.88, 0.77-1.00)	3.75 (0.91, 0.80-1.03)	2.2	1.9 (0.85, 0.70-1.02)	3.94	3.52 (0.89, 0.80-1.00)	4.35	3.99 (0.92, 0.83-1.01)	3.80 (0.87, 0.79-0.96)
GI Bleeding	1.02	1.51 (1.50, 1.19-1.89)	1.12 (1.10, 0.86-1.41)	2.2	3.2	0.86	0.76 (0.89, 0.70-1.15)	1.23	1.51 (1.23 (1.02-1.50)	0.82 (0.67, 0.53-0.83)
MI	0.53	0.74 (1.38, 1.00-1.91)	0.72 (1.35, 0.98-1.87)	1.1	0.9 (0.81, 0.63-1.06)	0.61	0.53 (0.88, 0.66-1.17)	0.75	0.70 (0.94, 0.74-1.19)	0.89 (1.19, 0.95-1.49)

Abbreviations: IQR, interquartile range; ROCKET AF, Rivaroxaban Once daily oral directed factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation.

dabigatran arm experienced more gastrointestinal (GI) bleeding and dyspepsia, the risk of intracranial and life-threatening bleeding was lower.[12] Overall, dabigatran at both doses was noninferior to warfarin in prevention of stroke and systemic embolism in patients with AF, with a superior safety profile at 110 mg twice daily.

Factor Xa inhibitors

Factor Xa inhibitors block the conversion of prothrombin to thrombin, preventing the final common pathway of the coagulation cascade; FXa is referred to as the "gatekeeper of coagulation."[29] The suitability of FXa in humans as a target was confirmed by large

clinical trials with fondaparinux, an indirect FXa inhibitor, shown to be safe and effective in acute coronary syndrome and pulmonary embolism.[34–36] After high-throughput screening and identification of the crystal structure of FXa,[37] novel oral *direct* FXa inhibitors were developed.[29,38]

Rivaroxaban

Rivaroxaban is a direct FXa inhibitor that was investigated in the ROCKET-AF (Rivaroxaban Versus Warfarin in Nonvalvular AF) trial. ROCKET-AF, a double-blind, double-dummy trial, enrolled 14,264 patients with nonvalvular AF and $CHADS_2 \geq 2$ (mean 3.47). Patients were randomized to rivaroxaban 20 mg (15 mg if creatinine clearance [CrCl] was 30-49 mL/min) or dose-adjusted warfarin (median TTR 58%). Rivaroxaban was noninferior to warfarin in preventing stroke and systemic embolism but failed to achieve superiority in the intention-to-treat analysis. Despite a lower rate of ICH and fatal hemorrhage with rivaroxaban, there was no reduction in death or ischemic stroke, and major GI bleeding events were more common in the rivaroxaban arm (3.2% vs 2.2%, $P < .001$).[13]

Apixaban

Apixaban is another direct FXa inhibitor that was investigated in the double-blind, double-dummy ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial. Patients with nonvalvular AF and $CHADS_2 \geq 1$ (mean 2.1) were randomized to apixaban 5 mg twice daily or to dose-adjusted warfarin (median TTR 66%). Apixaban was superior to warfarin in reducing stroke or systemic embolism and had significantly lower rates of major hemorrhage (2.13% vs 3.09%, $P < .001$) compared with warfarin. Furthermore, hemorrhagic stroke was reduced in the apixaban group (0.24% vs 0.47%, $P < .001$) and rates of GI hemorrhage were numerically, although not statistically less than in those treated with warfarin.[16]

Apixaban was also compared with aspirin in 5,599 patients with AF who were unsuitable for vitamin K antagonist (VKA) treatment in the AVERROES (Apixaban Versus Acetylsalicyclic acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) trial. Patients were randomized to either apixaban 5 mg twice daily or aspirin (81-324 mg/d) and were followed up for 1.1 years before the study was prematurely terminated due to superiority of apixaban over aspirin, with a 55% reduction in stroke or systemic embolism and similar bleeding rates.[15]

Edoxaban

Edoxaban was evaluated in the double-blind, double-dummy ENGAGE AF–TIMI 48 (Effective aNticoaGulation with factor xA next Generation in Atrial Fibrillation—Thrombolysis in Myocardial Infarction study 48), which enrolled 21,105 individuals with $CHADS_2$ score ≥ 2 (mean 2.8). Patients were randomized to once-daily high-dose edoxaban (60-or 30-mg dose reduced), once-daily low–dose edoxaban (30- or 15-mg dose reduced), or dose-adjusted warfarin (median TTR 68%). Of those randomized to edoxaban, 25.4% were dose reduced on prespecified risk factors known to increase drug exposure (CrCl 30-50 mL/min, weight ≤60 kg, or simultaneous use of verapamil or quinidine [P-glycoprotein inhibitors]).

In the intention-to-treat analysis, both high and low–dose edoxaban treatment arms were noninferior to warfarin in preventing stroke and systemic embolism. As with the other FXa inhibitors, the rate of hemorrhagic stroke was significantly reduced with high-dose edoxaban compared with warfarin (0.26% vs 0.47%, $P < .001$). The net clinical benefit for stroke, systemic embolism, major bleeding, and all-cause mortality significantly favored high-dose edoxaban over warfarin (hazard ratio [HR] 0.89, 95% CI 0.83-0.96).[14]

Edoxaban was also superior to warfarin in its safety profile. Major hemorrhage was significantly lower in the edoxaban arms, along with lower rates of life-threatening bleeding, intracranial bleeding, and major plus clinically relevant nonmajor bleeding. Although GI hemorrhage rates were greater in the high-dose edoxaban group (1.51%), it was less in the low-dose group (0.82%) compared with warfarin (1.23%).[14]

Meta-analyses of NOAC trial results

Meta-analysis of 4 RCTs investigating the NOACs in AF (N = 71,683) found that NOACs significantly reduced stroke and systemic emboli by 19% compared with warfarin; this was primarily driven by a reduction in hemorrhagic stroke rates (RR 0.49, 95% CI 0.38-0.64, $P < .0001$).[39] Although NOACs increased the risk of GI bleeding (RR 1.25, 95% CI 1.01-1.55, $P = .04$), they significantly improved rates of ICH (RR 0.48, 95% CI 0.39-0.59, $P < .0001$).[39] NOACs also significantly reduced all-cause mortality (RR 0.90, 95% CI 0.85-0.95, $P = .0003$). For low-dose NOACs, stroke or systemic embolic events were broadly equivalent to warfarin (RR 1.03, 95% CI 0.84-1.27, $P = .74$) with a safer bleeding profile (RR 0.65, 95% CI 0.43-1.00, $P = .05$), but with more ischemic strokes (RR 1.28, 95% CI 1.02-1.60, $P = .045$).[39]

Presently, none of the individual NOACs have been studied in direct head-to-head comparisons. Indirect comparison between trials is complicated because of baseline differences, inclusion criteria (particularly stroke risk), $CHADS_2$ score, achieved TTRs, and varying dose reduction protocols.[40] Despite this, individual NOACs exhibit particular characteristics that may support their use in specific patient populations.

Individualized anticoagulation: which agent in which patient?

In the absence of direct comparison data, selecting the most appropriate agent can be based on shared decision making, taking into account some limited information from indirect comparisons, adverse event profiles, specific pharmacokinetic properties, drug-drug interaction profile, renal and hepatic function, other comorbidities, and the TTR if already treated with a VKA.[17,41] Accounting for individualized risk of stroke and bleeding, as described in the CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack; vascular disease, age 65-74 years, and sex category) and a validated bleeding score, respectively is paramount (Table III). Limitations of $CHADS_2$ score with its failure to account for many common stroke risk factors including an intermediate age category, vascular disease, and female gender[42,43] led to inaccurate labeling of many patients as low risk, despite many who were experiencing >1.5% annual stroke rate.[44] The CHA_2DS_2-VASc score better stratifies patients with AF who are truly low-risk and a score of 0 (male) or 1 (female) who should not be offered anticoagulation as the risks outweigh the benefits.[23,45,46] Scores ≥1 (male) or ≥2 (female) should undergo assessment of bleeding risk prior to starting anticoagulation.[9]

Anticoagulation is underused to varying extents in all populations, primarily owing to physician anxiety regarding hemorrhage risk and poor patient adherence. The GARFIELD (Global Anticoagulant Registry in the FIELD—Atrial Fibrillation) registry of 17,184 newly diagnosed AF patients reported anticoagulation use in 60.8% of eligible individuals, and of those CHA_2DS_2-VASc ≥2, more than 35% were not anticoagulated.[47] A more recent report of the PREFER in AF (PREvention oF thromboembolic events—European Registry in Atrial Fibrillation) registry reported that 11.2% were on antiplatelet agents alone with only 6.5% not on any antithrombotic therapy.[48] Similar data from GLORIA-AF (Global Registry on Long-Term Oral Antithombotic Treatment in Patients with Atrial Fibrillation) in a North American subset indicate that 21.9% of patients with paroxysmal AF and a CHA_2DS_2-VASc score of 2 were being undertreated on aspirin or given no anticoagulant treatment at all.[49] Although the uptake of oral anticoagulation is improving, antiplatelet therapy alone is still commonly prescribed.

Chronic users of warfarin with labile INR experience lower rates of thromboembolism with NOACs,[13] and NICE recommend reassessing anticoagulation in all patients with TTR <65%.[9] Optimal TTR is defined as >70%,[50,51] and poor control is associated with increased bleeding and thromboembolic risk.[52] When TTR drops below 50%, stroke and bleeding risk is worse than those in untreated patients.[53,54] In assessment, poor control can be defined in a 6-month period by 1 INR value >8.0, 2 INR values >5.0, or 2 INR values <1.5 (after the first 6 weeks of treatment). However, it is essential to identify the reasons for this instability. If secondary to poor adherence, warfarin remains the better choice of anticoagulation, because of the easy ability to test the anticoagulation status. However, if compliance is optimal and the TTR remains low, NOACs are recommended[55] (Figure 2).

Table III. Risk assessment scores for anticoagulation in AF[46,91]

Definition	Score
CHA_2DS_2-VASc	
Congestive heart failure	1
Hypertension	1
Age >75 y	2
Diabetes mellitus	1
Stroke/Transient ischemic attack	2
Vascular disease (prior MI, PAD, aortic plaque)	1
Age 65-74 y	1
Female sex	1
HAS-BLED	
Hypertension	1
Abnormal renal and liver function	1 or 2
Stroke	1
Bleeding	1
Labile INRs	1
Elderly >65 y	1
Drugs or alcohol (1 point each)	1 or 2
SAMe-TT_2R_2	
Sex (female)	1
Age (<60 y)	1
Medical history*	1
Treatment (interacting medications)†	1
Tobacco use (in last 2 y)	2
Race (nonwhite)	2

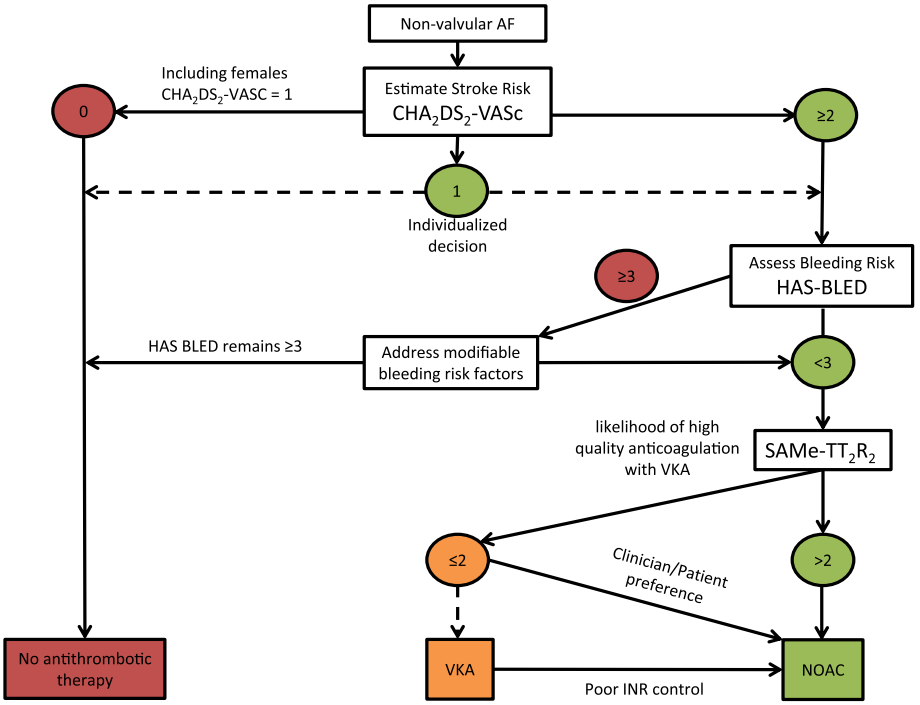
*Two of the following: hypertension, diabetes, coronary artery disease, myocardial infaction, peripheral arterial disease, congestive heart failure, prior stroke, pulmonary, hepatic or renal disease.
† For example, amiodarone for rhythm control.

Erratic INR control is associated with numerous patient-level factors including polypharmacy, multiple hospitalizations, alcohol or drug abuse, cancer, dementia, and bipolar disorder.[56] The SAMe-TT_2R_2 (sex [female], age <60 years, medical history, treatment including interacting medications, tobacco use, race [nonwhite]) is a validated score to assist prescribers in identifying patients likely to attain high-quality anticoagulation on warfarin, with scores >2 associated with poor attainment.[57,58]

In the first month of initiating warfarin therapy, the risk of stroke increases by 71%, due in part to the transient hypercoagulable state and a suboptimal INR.[59] A SAMe-TT_2R_2 score ≤2 prior to starting anticoagulation should prompt consideration of warfarin or a NOAC,[60] whereas scores >2 predict greater time outside the TTR and careful monitoring will be needed.[61]

A summary of the clinical opinion for selecting between anticoagulants is referred to in Figure 3. This is based on the patients' characteristics in the absence of

Figure 2



Choice of anticoagulant. Based on the ESC guidelines update 2012 addressing the balance of stroke vs bleeding risk in patients with nonvalvular AF.[23] Color: green represents those favoring NOAC, amber indicates that VKAs should be considered, and red indicates that anticoagulation is not required. Solid line is the preferred option and dashed line is an alternative option.

direct head-to-head trials. Information from indirect comparison trials, subgroup analyses, adverse event profiles, and trials within non-AF population groups have been used in reaching this form of clinical consensus. Although Figure 3 has not been prospectively validated, it is a guide to assist clinicians to identify the most appropriate agent for their patients. Clinical decisions relating to agent selection should take account of individual presentations and the local regulatory body approval.

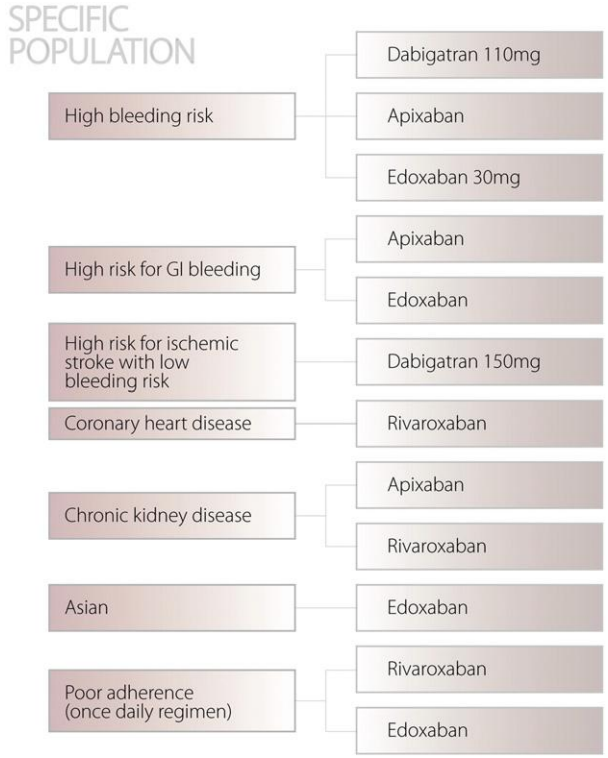
Chronic kidney disease

Approximately 1 in 3 patients with AF have proteinuria or chronic kidney disease (CKD),[62] which is associated with both increased risk of stroke and hemorrhage, the latter due to uremia-induced platelet dysfunction and coagulation dysregulation.[63] Although warfarin therapy confers a significant reduction in stroke risk in CKD,[64] it has a poor safety profile in stage 4 CKD with more major bleeding events compared with stage 3 CKD.[65] Furthermore, patients with both stage 3 and 4 CKD spend more time above the target range of INR, potentially increasing the risk of hemorrhage.[65]

Among patients with AF and in end-stage renal disease (ESRD) undergoing dialysis, those treated with warfarin not only experienced a higher bleeding risk but also failed to benefit from a reduction in stroke risk (adjusted HR 1.14, 95% CI 0.78-1.67).[66] This was supported by a propensity-matched study of hemodialysis patients in AF that demonstrated that warfarin users experienced twice the hemorrhagic risk (HR 2.38, 95% CI 1.15-4.96) with similar ischemic stroke rates as non-warfarin users.[67] Another retrospective cohort study among patients with ESRD demonstrated an association between warfarin use and increased overall stroke risk (HR 1.93, 95% CI 1.29-2.90).[68]

All the NOACs are dependent in part on renal elimination; accordingly patients with CKD are at risk for increased drug exposure with risk of hemorrhage.[69] Post hoc analysis of the RE-LY trial showed that stroke or systemic embolism rates were lower with dabigatran 150 mg than warfarin across all levels of renal function; however, significantly reduced rates of major bleeding were observed only in patients with a glomerular filtration rate of ≥80 mL/min.[70] The Food and Drug Administration (FDA) approved a reduced dabigatran dose of 75 mg twice daily for those with CrCl 15-30 mL/min, whereas the European Medicines Agency (EMA) approved 75 mg bd for those with CrCl 30-50 mL/min but did not approve it for CrCl <30 mL/min.[71,72]

Figure 3



Non–vitamin K antagonist oral anticoagulant selection in different patient populations. Opinions based on indirect comparitor trials, subgroup analyses, and adverse event rates (in the absence of direct comparison head-to-head trials). Modified from Savelieva and Camm.[41]

Patients with CrCl 30-49 mL/min in the ROCKET-AF trial were randomized to a reduced 15 mg once daily dose of rivaroxaban. No differences were reported between warfarin and rivaroxaban arms in the primary efficacy or safety end points. However, significantly lower rates of fatal bleeding occurred in the rivaroxaban group.[73] For AF patients with CrCl 30-49 mL/min, a lower dose of 15 mg once daily is recommended.[74] Importantly, patients with stage 4 CKD or worse were excluded from both the RE-LY and ROCKET-AF trials.[13,15]

Despite being predominantly eliminated by the liver,[75] apixaban was dose reduced in ARISTOTLE (Apixaban for Reduction in Stroke and Other ThrombemboLic Events in atrial fibrillation) to 2.5 mg if 2 of 3 factors were present: serum creatinine ≥1.5 mg/dL, age ≥80 years, or body weight ≤60 kg. Subgroup analysis revealed that apixaban was more efficacious than warfarin irrespective of renal function, indicating that apixaban may be a desirable agent in CKD.[76] Patients with moderate (CrCl 30-50 mL/min) or severe (CrCl ≤30 mL/min) renal impairment had a greater reduction in major bleeding with apixaban compared with warfarin.[16] The FDA has approved apixaban 5 mg twice daily in patients with ESRD who are maintained on stable hemodialysis, although clinical data for use in this setting are limited.[77]

Some 50% of edoxaban is excreted via the renal route, and the EMA has approved edoxaban 60 mg once-daily with dose reduction to 30 mg in patients with CrCl (15-50 mL/min), and have not recommended the agent in patients with ESRD (CrCL <15 mL/min) or on dialysis.[78] Edoxaban was indirectly compared with the other 3 NOACs in a recent meta-analysis of 5 studies in relation to renal function.[79] In moderate renal impairment (CrCl 25-49 mL/min), edoxaban at both high and low-doses, had less major bleeding compared with dabigatran (both doses), rivaroxaban but not apixaban. Although low-dose edoxaban was favorable in all indirect comparisons for safety, it was inferior to dabigatran 150 mg for efficacy outcomes (HR 0.48, 95% CI 0.30-0.77). High-dose edoxaban was not significantly different in any indirect efficacy comparison in moderate renal impairment. In mild renal impairment (CrCl 50-79 mL/min), high-dose edoxaban was not significantly different in any indirect efficacy or safety comparisons. Furthermore, low-dose edoxaban was favorable in all indirect safety comparisons, but at this lower dose, dabigatran 150 mg and rivaroxaban 10 mg were superior in efficacy outcomes. These data should be interpreted with care and acknowledgement of the inherent limitations associated with indirect comparisons of different trials.

In all studies, regardless of treatment allocation, patients with CKD had higher rates of stroke or major hemorrhage events compared with those with normal renal function.[12,13,15,16,73,80] With limited randomized data in this population regarding reduced dose NOAC regimens and warfarin, further work is required to elucidate the optimal anticoagulation strategy. Assessment of renal function is mandatory prior to initiating an NOAC and should be monitored annually in those with CrCl >50 mL/min and 2 to 3 times per year in those with CrCl 30-49 mL/min.[23]

Elderly

Atrial fibrillation increases in prevalence with age and affects around 20% of individuals older than 85 years.[10,81] Elderly patients with AF have a greater burden of cardiovascular risk factors[82,83] and excess risk of stroke as reflected in the CHA_2DS_2-VASc score. Rates of anticoagulation in the elderly are consistently poorer relative to a younger population and physician-cited reasons for this include prior falls, hemorrhage, and patient refusal.[84] It has been estimated that a patient would have to fall more than 295 times per year for the risk of ICH to offset the benefit of warfarin,[85] and falls risk alone should not be a reason to withhold anticoagulation.[9]

There are concerns over the use of NOACs in patients older than 85 years with multiple comorbidities,

polypharmacy, and reduced compliance. However, NOACs have many practical advantages in the elderly: fewer drug interactions, predictable pharmacology, and reduced need for monitoring. Meta-analysis of 25,031 patients 75 years or older enrolled into RCTs comparing rivaroxaban, apixaban, and dabigatran with conventional therapy demonstrated NOACs were superior in prevention of stroke or systemic embolism, without causing an excess of bleeding.[86] Trials of apixaban, rivaroxaban, and edoxaban demonstrated no interaction of age with incident major bleeding[87]; however, a post hoc analysis of RE-LY reported a significant age interaction with a trend toward more bleeding with dabigatran 150 mg twice daily As a consequence, the European Summary of Product Characteristics for dabigatran states that age ≥75 years is associated with increased bleeding risk and patients 80 years or older should receive the lower dabigatran dose (110 mg twice daily).[88] In the ARISTOTLE trial, apixaban was used at a reduced dose of 2.5 mg in patients with 2 or more of the following criteria: ≥80 years, body weight ≤ 60 kg, and serum creatinine ≥1.5 mg/dL, and this was replicated in the FDA approval.[16,77]

Bleeding prone

Numerous calculators are available to score bleeding risk including ATRIA,[89] HEMORR$_2$HAGES,[90] and HAS-BLED.[91] HAS-BLED has been shown to have the best predictive value of bleeding risk,[92,93] with a score ≥3 indicating high risk. This should prompt care providers to modify reversible risk factors including hypertension, polypharmacy including concomitant aspirin or nonsteroidal anti-inflammatory drug use, and a labile INR. Overestimation of bleeding risk represents a real clinical problem and a HAS-BLED score ≥3 should not be viewed as an absolute contraindication[94,95]; 4 of the 8 points in the HAS-BLED score are modifiable.

Receiver operator curve analyses suggest that all 3 scores have an area under the curve of <0.7, indicating modest performance, and for this reason, all were excluded from American Heart Association guidelines.[17,96] Interestingly, individuals with a high HAS-BLED score experienced a greater absolute risk reduction in stroke risk with warfarin.[97] Accordingly, a large observational study suggests that adjusted net clinical benefit favors anticoagulation for all AF patients, except those at very low risk for ischemic stroke (CHA_2DS_2-VASc = 0) and moderate-high bleeding risk.[98]

Overall, the 4 NOACs, when compared with warfarin, reduce ICH but increase GI bleeding.[39] Differences exist between individual NOACs in terms of the type of hemorrhage. Although 150 mg twice daily dabigatran is equivalent to the bleeding risk with warfarin (RR 0.93, 95% CI 0.81-1.07, $P = .31$), 110 mg twice daily dabigatran (RR 0.80, 95% CI 0.69-0.93, $P = .003$) exhibits a lower major hemorrhage risk.[12] However, after FDA approval of dabigatran, more than expected reports of serious and fatal bleeding events associated were submitted. The FDA reviewed drug safety reports, and although the rate of bleeding after approval could have exceeded that expected from RE-LY, it is likely that by virtue of the novelty of the drug alone, high reporting rates of adverse events were elicited. When comparing insurance claim databases, bleeding rates associated with dabigatran did not appear to be higher than that seen with warfarin.[99] Although a propensity-matched cohort study comparing dabigatran to warfarin in elderly patients with AF demonstrated an increased risk of major GI hemorrhage with dabigatran, there was a reduced risk of ischemic stroke, ICH, and death.[100]

Gastrointestinal bleeding is of particular concern due to the associated mortality of 7%.[101] Factors that increase an individual's risk of GI bleeding include peptic ulcer disease, alcohol abuse, nonsteroidal anti-inflammatory drug use, previous GI bleed, advanced liver disease, and age over 60 years. Subsequently, individuals with these risk factors should be anticoagulated with caution having addressed all modifiable risk factors.[102]

In ROCKET-AF, 20 mg rivaroxaban daily was associated with similar rates of major and clinically relevant non-major bleeding in warfarin-treated patients (RR 1.03, 95% CI 0.96-1.11); however, fatal bleeding was less frequent with rivaroxaban.[13] The rate of major hemorrhage with apixaban 5 mg twice daily was 2.13% vs 3.09% per year with warfarin,[16] and hemorrhagic stroke was 0.24% with apixaban vs 0.47% per year with warfarin. High-dose edoxaban (RR 0.80, 95% CI 0.71-0.91) and low-dose edoxaban (RR 0.47, 95% CI 0.41-0.55) significantly reduced major hemorrhage compared with warfarin. Of note, low-dose edoxaban is the only NOAC to be associated with significantly less GI bleeding (RR 0.67, 95% CI 0.53-0.83).[14] Furthermore, an imputed-placebo analysis and indirect comparisons between NOACs revealed that low-dose edoxaban is associated with a lower risk of major hemorrhage than other NOACs, although this is potentially counterbalanced by a lower efficacy in thromboembolism prevention.[103] Taken together, patients at high risk for hemorrhage should avoid high-dose dabigatran and rivaroxaban. Low-dose dabigatran, rivaroxaban, apixaban, and edoxaban are safer choices in patients with increased risk for GI hemorrhage. Of these, from an indirect comparison, the dosing strategy with edoxaban has proven to maintain efficacy while lowering major bleeding events.[40]

Coronary heart disease

The ACTIVE W and ACTIVE A trials demonstrated that 14% to 17% of AF patients have had a prior myocardial infarction (MI),[104,105] a group in whom antiplatelet and anticoagulant prescriptions are common. Prospective analysis of 7,243 patients with AF demonstrated 95.3% (629/660) of patients on dual antiplatelet, and

anticoagulation therapy did not have an accepted indication and exposed patients to inappropriate bleeding risks.[106] The combination of anticoagulation and aspirin is associated with greater incidence of major hemorrhage; however, this risk is significantly lower with NOACs than warfarin.[12–15,80]

In the setting of coronary artery stenting, a reduction in mortality and major cardiac events was observed with concomitant oral anticoagulation.[107] In patients with AF presenting with acute coronary syndrome, a variable period of triple therapy is recommended (oral anticoagulant plus aspirin plus clopidogrel), followed by dual therapy (single antiplatelet agent) up to 1 year after the acute coronary syndrome and its immediate management.[23] After this, only oral anticoagulation monotherapy is recommended in these patients.

Concerns persist regarding use of dabigatran in patients with coronary artery disease because dabigatran at both doses in RE-LY was thought to be associated with significantly higher rates of MI versus warfarin.[12] Reanalysis to include silent MI not previously identified found no significant difference in MI rates.[108] A further post hoc analysis from RE-LY using a composite of MI, unstable angina, cardiac arrest, and cardiac death demonstrated a nonsignificant reduced risk with dabigatran compared with warfarin.[109] However, meta-analysis of 7 trials of dabigatran versus other anticoagulants demonstrated increased risk of MI or acute coronary syndrome (odds ratio [OR] 1.33, 95% CI 1.03-1.71, P = .03), but with a reduction in all-cause mortality (OR 0.89, 95% CI 0.80-0.99, P = .04).[110] Clearly, these results are contradictory; however, dabigatran is best used with caution in patients at high risk for coronary events. In a large-scale nationwide postapproval cohort study of "real-world AF patients," switching to dabigatran increased the risk of MI compared with continuing warfarin in the early phase after switching.[111] However, the overall incidence after 14 months of follow-up showed that MI was lower with dabigatran at both doses compared with warfarin.[112] Furthermore, a recent propensity-matched analysis of 134,414 elderly patients in AF demonstrated no significant difference in MI rates between dabigatran and warfarin-treated patients.[100]

Regarding the other NOAC trials, the rates of MI reported were equivalent to warfarin for rivaroxaban (HR 0.81, 95% CI 0.63-1.96), apixaban (HR 0.88, 95% CI 0.66-1.17), and high-dose edoxaban (0.94, 95% CI 0.74-1.19).[13,16] Of these NOACs, rivaroxaban was shown to have the greatest trend toward reduced MI; however, further studies are required to further assess NOAC safety and efficacy in this population.[113]

Heart failure

Patients with HF are more likely to develop AF, which is itself an independent risk factor for development of HF.[114] Heart failure, even in sinus rhythm, is associated with ischemic stroke. In patients with AF, HF has been linked with increased risk of stroke and death irrespective of left ventricular systolic function.[115] Congestive heart failure is included in the CHA_2DS_2-VASc score representing a higher stroke risk, although this criterion refers only to moderate-to-severe systolic dysfunction (ie, HF with reduced ejection fraction [HFrEF]) or acute decompensated HF requiring hospitalization, regardless of ejection fraction.[116] This represents a change from the $CHADS_2$ score where decompensated HF only was included,[44] and is supported by evidence to suggest that patients with HFpEF exhibit the same risk of embolic events as those with HFrEF.[117]

Stroke is responsible for 4% of deaths in patients with concomitant AF and HFrEF.[118] Results from the Belgrade AF study showed that patients with AF are more likely to progress from paroxysmal to permanent AF if HF is also present, which may partly explain the increased risk of stroke.[119]

In RE-LY and ARISTOTLE, patients with HF experienced increased rates of thromboembolism in comparison with ROCKET-AF.[12,13,16] In a meta-analysis of these studies, NOACs were superior to warfarin for efficacy in patients without HF, but no difference was observed among patients with HF (OR 0.91, 95% CI 0.78-1.06).[120] Subgroup analysis of ENGAGE AF-TIMI 48 showed efficacy of edoxaban at both low- and high-dose in patients with and without HF.[121] Despite these results, further studies are required to fully elucidate the impact of NOACs in the different HF subgroups (HFrEF and HFpEF and their respective etiologies). What is clear is that AF patients with HF exhibit increased risk of stroke, and physicians, in addition to managing the HF, should be actively encouraged to anticoagulate these vulnerable individuals regardless of their ejection fraction.[122,123]

Asian patients

Asian populations have a lower prevalence of AF relative to the West, and AF results in a more modest 3-fold increase in stroke risk.[124–127] However, Asians appear to be at greatest overall risk for both hemorrhagic and ischemic stroke, secondary to a higher prevalence of risk factors.[128]

The risk of stroke and hemorrhage is inconsistent among different Asian subgroups; East Asians (China, Japan, Korea, Laos, Thailand, and Vietnam) appear more susceptible to ICH compared with South Asians (India, Pakistan).[129] This might be explained by a higher warfarin sensitivity attributed to the homozygous H1 genotype of the vitamin K epoxide reductase complex 1, which has preponderance among East Asian patients.[130]

As a consequence of the perceived increase in bleeding risk among Asian patients, warfarin is underprescribed, with prescription rates roughly half that of Europeans,

irrespective of stroke risk.[131] Instead, aspirin is commonly prescribed despite data reporting that 150 to 200 mg aspirin is neither safe nor effective in Japanese patients with nonvalvular AF.[132]

A recent meta-analysis of NOACs among Asians demonstrated that dabigatran 150 mg twice daily significantly reduced stroke and systemic emboli, with the other NOACs showing a nonsignificant trend toward reducing events, except low-dose edoxaban. All the NOACs, with the exception of rivaroxaban 20 mg, significantly lowered hemorrhagic strokes among Asians. High-dose edoxaban significantly reduced all-cause mortality among Asian patients compared with warfarin, with nonsignificant trends toward reduced mortality noted with dabigatran 150 mg, rivaroxaban, and low-dose edoxaban. For safety outcomes, all the NOACs, except rivaroxaban 20 mg, significantly reduced major bleeding and all bleeding events. Intracranial hemorrhage was reduced by all NOACs compared with warfarin and none increased GI bleeding.[133] In the predefined Asian subgroup of ENGAGE AF–TIMI 48, high–dose edoxaban led to reduced incidence of stroke or systemic embolism (1.86% vs 2.37%), whereas both low and high-dose led to significantly lower major hemorrhage rates (1.87% and 3.51% vs warfarin 4.12%, respectively), making edoxaban an attractive agent in this population.

The J-ROCKET-AF trial investigated rivaroxaban in Japanese patients who were intentionally excluded from the main ROCKET AF trial, owing to reduced INR targets of 1.6 to 2.6 in Japanese AF patients 70 years or older. Rivaroxaban was noninferior to warfarin in stroke prevention, and no significant difference in bleeding between treatment arms was observed.[134] In contrast to ROCKET-AF, no increase in GI bleeding was seen, which may be due in part to ethnic differences or the small number of patients recruited. The Japanese Circulation Society and Asia-Pacific Heart Rhythm Society support the use of NOACs as first-line agents in stroke prevention in Asians with AF.[135,136]

Patient adherence

Non–vitamin K antagonist oral anticoagulants have shorter half-lives than warfarin, mandating good adherence if patients are to remain protected.[12–14,16] Physicians can improve compliance through education around the risks of untreated AF. In the UK, NICE recently released a patient decision aid that helps portray the embolic risk in AF with the associated hemorrhage risk with anticoagulation, based on an individual's CHA_2DS_2-VASc score.[137] Of concern, in a UK survey of 119 inpatients with AF on warfarin, only 63% were aware of their condition, and of those that were aware, 61% felt AF was not serious with 48% of patients unable to explain why they were anticoagulated.[138]

A further questionnaire in 172 inpatients assessed thresholds for bleeding events that they would be willing to endure on anticoagulation after providing each patient their individualized risk score. They found that patients required at least a 0.8% annual absolute risk reduction in stroke (number needed to treat = 125) and were willing to endure 4.4 major bleeds to prevent one stroke in order to agree to initiate anticoagulation therapy.[139] These findings support earlier work that found that patients place more value on stroke prevention than on hemorrhage avoidance.[140] The mismatch between patient preference and physician anxiety regarding bleeding risk needs to be overcome through shared management of these risks in a physician-patient partnership.

Cost-effectiveness

In the current economic climate, cost-effectiveness will be a key consideration. Results from RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE AF–TIMI suggest that NOACs are associated with lower medical costs (excluding drug costs) relative to warfarin,[141–144] and this will be greatest among patients where INR control is poor.[145] However, cost-effectiveness is dependent on local factors including resource availability, pricing, and TTR achieved by the specific anticoagulation service.[145,146] In any event, the immediate cost of switching large numbers of patients from stable therapy with warfarin to NOAC therapy is considerable and only yields an economic advantage after several years of resulting stroke reduction.

Conclusion

The overall burden of AF is rising commensurate with the options to manage it. Despite clear guidance and overwhelming evidence supporting the benefits of anticoagulation, undertreatment persists. Non–vitamin K antagonist oral anticoagulants are as effective as warfarin in prevention of stroke, whereas simultaneously reducing rates of ICH and life-threatening bleeding. Patient involvement in shared decision making around the most appropriate agent for anticoagulation can be facilitated by education on individualized thromboembolic and bleeding risks.

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Contributors

O.J.Z. performed the literature search and prepared the initial draft of the manuscript. A.J.C. contributed to the critical revision of the manuscript. Both authors have approved the final article.

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