Anticoagulation for Atrial Fibrillation

A Review of Current Literature and Views

Chengyue Jin, MD, Can Cui, MD, PHD,† Matthew Seplowe, DO,* Kyu-In Lee, MD,* Rathnamitreyee Vegunta, MD,* Bo Li, MD,* William H. Frishman, MD,* and Sei Iwai, MD‡*

Abstract: Atrial fibrillation is a common supraventricular tachyarrhythmia with uncoordinated atrial activation and ineffective atrial contraction. This leads to an increased risk of atrial thrombi, most commonly in the left atrial appendage, and increased risks of embolic strokes and/or peripheral thromboembolism. It is associated with significant morbidity and mortality. To meet the concerns of thrombi and stroke, anticoagulation has been the mainstay for prevention and treatment thereof. Historically, anticoagulation involved the use of aspirin or vitamin K antagonists, mainly warfarin. Since early 2010s, direct oral anticoagulants (DOACs) including dabigatran, rivaroxaban, apixaban, and edoxaban have been introduced and approved for anticoagulation of atrial fibrillation. DOACs demonstrated a dramatic reduction in the rate of intracranial hemorrhage as compared to warfarin, and offer the advantages of absolution of monitoring therefore avoid the risk of hemorrhages in the context of narrow therapeutic window and under-treatment characteristic of warfarin, particularly in high-risk patients. One major concern and disadvantage for DOACs was lack of reversal agents, which have largely been ameliorated by the approval of Idarucizumab for dabigatran and Andexanet alfa for both apixaban and rivaroxaban, with Ciraparantag as a universal reversal agent for all DOACs undergoing Fast-Track Review from FDA. In this article, we will be providing a broad review of anticoagulation for atrial fibrillation with a focus on risk stratification schemes and anticoagulation agents (warfarin, aspirin, DOACs) including special clinical considerations.

Key Words: atrial fibrillation, anticoagulation, embolic stroke, hemorrhage

(*Cardiology in Review* 2024;32: 131–139)

Atrial fibrillation (AF) is a common supraventricular tachyarrhythmia with uncoordinated atrial activation and ineffective atrial contraction. It is multifactorial in etiology and can have a broad spectrum of symptoms including fatigue, palpitations, dyspnea, lightheadedness, syncope, or exertional intolerance. The prevalence of AF increases with advancing age with a prevalence of 1% in people less than 60 years of age and 12% in people aged 75–84 years.[1] AF contributes to significant morbidity and mortality with frequent hospitalizations, hemodynamic abnormalities, and thromboembolic events; with an estimate of more than 99,000 deaths per year and total hospitalizations greater than 467,000 annually.[2,3] AF is associated with a fivefold increased risk of stroke,[4] threefold risk of heart failure,[5–7] and twofold risk of dementia and mortality.[4,8] This in turn results in an increase of about 26 billion dollars to the United States healthcare expenditure annually and an estimate of adding a differential of $8,700 per year for AF patients as compared to non-AF patients.[2,3]

AF is commonly diagnosed on electrocardiogram with irregular R-R intervals and absence of distinct repeating P waves with irregular rapid atrial activity. It often occurs because of structural and/or electrophysiological abnormalities that alter atrial tissue to promote abnormal impulse formation and propagation. This leads to an increased risk of atrial thrombi, most commonly in the left atrial appendage, and increased risks of stroke and/or peripheral thromboembolism.[9] To mitigate the risk of thrombi and stroke, anticoagulation has been the mainstay for prevention and treatment thereof. Historically, anticoagulation involved use of aspirin or vitamin K antagonists (VKA), mainly warfarin.[10] Warfarin has proven to be a clinically challenging treatment modality given the requirement for close monitoring of International Normalized Ratio (INR) and risk of major bleeding such as intracranial hemorrhage. Anticoagulation has been associated with nearly doubling in relative rate of intracranial hemorrhage (0.46% vs 0.23%) but in the context of low absolute risk of intracranial hemorrhage.[11]

VKA has been largely supplanted with direct oral anticoagulants (DOAC) for stroke reduction in patients with nonvalvular AF. Oral anticoagulants such as dabigatran, rivaroxaban, apixaban, and edoxaban were noninferior to VKA.[12] DOACs had dramatic reduction in rate of intracranial hemorrhage as compared to VKA,[13–15] and do not require intermittent monitoring to avoid the risk of hemorrhages in the context of narrow therapeutic window, particularly in high-risk patients.[16] Several guidelines have been published that specifically address the use of DOACs in patients with nonvalvular AF.[17–19]

Risk stratification schemes were developed to help guide anticoagulation strategies. The $CHADS_2$ risk scheme was based on risk factors of heart failure, hypertension, age, diabetes mellitus, and prior stroke. It provided a modest predictive value for stroke and thromboembolism with categories of either low-, moderate-, or high-risk patients. The CHA_2DS_2-VASc scheme was subsequently developed and added risk factors of vascular disease and sex with more focus on the age risk factor. In a study of 80,000 AF patients, CHA_2DS_2-VASc performed similarly compared to $CHADS_2$ in predicting thromboembolism and identified patients who are truly at low risk and avoid stratifying into the intermediate/moderate risk category.[20] Other risk scheme have also been introduced but less commonly utilized including CHA_2DS_2-VASc–R (R as African American), R_2 (creatinine)-$CHADS_2$, and ATRIA stroke risk score.[21–23] A summary of different risk stratification models is provided in Table 1. On the contrary, bleeding risk schemes were developed to help balance the benefits and risks of anticoagulation. Initially HEMORRHAGES was commonly used until the HAS-BLED score became more popular with its similar performance and less complicated use.[24,25]

In this article, we will be providing a broad review of anticoagulation for AF with a focus on risk stratification schemes and anticoagulation agents (warfarin, aspirin, and DOACs) including special considerations of clinical importance.

From the *Department of Medicine, Westchester Medical Center, Valhalla, NY; †Department of Immunobiology, School of Medicine, Yale University, New Haven, CT; and ‡Department of Cardiology, Westchester Medical Center, Valhalla, NY.

The authors declare no conflicts of interest.

Correspondence: Sei Iwai, MD, FACC, FHRS, Department of Cardiology, Westchester Medical Center, 914.909.6900, 100 Woods Road, Valhalla, NY 10595. E-mail: sei.iwai@wmchealth.org.

ISSN: 1061-5377/24/3202-131139
DOI: 10.1097/CRD.0000000000000489

TABLE 1. Stroke Risk Assessment Tools

	Heart Failure	Hypertension	Age	Diabetes	Prior Stroke or Systemic Embolism	Vascular Disease	Female	Chronic Kidney Disease	Proteinuria	African American
$CHADS_2$	1	1	1 (≥75 years)	1	2	n/a	n/a	n/a	n/a	n/a
CHA_2DS_2-VASc	1	1	1 (65–74 years) 2 (≥75 years)	1	2	1	1	n/a	n/a	n/a
CHA_2DS_2-VASc–R	1	1	1 (65–74 years) 2 (≥75 years)	1	2	1	1	n/a	n/a	1
R_2 -$CHADS_2$	1	1	1 (≥75 years)	1	2	n/a	n/a	2 (eGFR < 60)	n/a	n/a
ATRIA	1	1	0–6 (no prior stroke) 7–9 (with prior stroke)	1	n/a	n/a	1	1 (eGFR < 45 or ESRD)	1	n/a

eGFR indicates estimated glomerular filtration rate; ESRD, end-stage renal disease.

VITAMIN K INHIBITORS

Nonrheumatic AF is one of the most common cardiac maladies affecting people across the globe. Until 2010, choice of anticoagulation had been limited to VKA, namely warfarin, and antiplatelet agents such as aspirin.[26] While the latter has not proven benefit in reducing the number of cerebrovascular events, warfarin remains an established treatment for prevention of ischemic stroke.[27] However, it is not without significant drawbacks, including the need for consistent medical follow up and monitoring to maintain a narrow therapeutic window as well as multiple food and drug interactions due to its metabolism via the Cytochrome P450 enzyme system. The benefits of the medication are proportional to the patient's time spent within the therapeutic range (TTR) of INR of 2.0–3.0 in most clinical scenarios and higher goals with special considerations.[26] Warfarin has consistently shown to decrease the risk of stroke in patients with AF (a 68% reduction in risk).[28] This benefit is also extended to elderly patients over 70 years of age.[29]

Coagulation factors II, VII, IX, X, Protein C and S are synthesized in the liver. Reduced vitamin K (hydroquinone) donates a pair of electrons to facilitate the enzymatic carboxylation (activation) of these factors and itself is oxidized to an inactivated form (quinone). Quinone is reactivated by vitamin K epoxide reductase complex 1 (VKORC1) by receiving a pair of electrons from nicotinamide adenine dinucleotide (NADH) and return to hydroquinone. Warfarin functions by competitively antagonizing VKORC1, thus preventing the recycle of the active (reduced) form of the vitamin K and activation of vitamin K-dependent clotting factors.[30] Changes INR can be seen as early as 24 hours and the medication lasts for 2–5 days. It is metabolized in the hepatic system and is subject to the Cytochrome P450 system, primarily by CYP2C9.[31]

Due to the differing half-lives of the various clotting factors, warfarin initially has a pro-thrombotic effect, by blocking proteins C and S, followed by a delayed antithrombotic effect, through the inhibition of coagulation factors II, VII, IX, and X.[32] Due to the initial procoagulant effect of VKA, they often require "bridging" or the administration of a rapid-acting parental anticoagulation agent in the first few days of use. Bridging can be discontinued once therapeutic level of warfarin is reached. A full review of bridging will not be discussed in this review.

Warfarin is taken orally, usually at a starting dose of 5–10 mg daily. INR is monitored over the course of days and doses are adjusted based on this serum monitoring. Warfarin is primarily metabolized through the P450 system.[10] Induction or inhibition of the isoenzymes involved with warfarin's metabolism can potentially increase the INR significantly.[33] Furthermore, alterations in vitamin K-rich food such as green leafy vegetables consumption can create significant fluctuations in the INR.[34]

Hemorrhage is the most significant adverse effect associated with warfarin and is directly related to the level of INR; the risk of hemorrhage is increased if the INR is greater than 5.[33] Risk factors for warfarin-related hemorrhage include advanced age, serious comorbid conditions including cancer, chronic kidney disease (CKD), liver dysfunction, hypertension, prior stroke, alcohol abuse, and the concomitant use of antiplatelet or other drugs.[33] In the event of hemorrhage, the anticoagulant effects of warfarin can be reversed with the administration of vitamin K, fresh frozen plasma (FFP), or prothrombin complex concentrates.[24,35] In addition, recombinant factor VIIa (rfVIIa) has been suggested as a possible reversal agent. While the use of rfVIIa has been demonstrated to provide a rapid reduction in the INR, its use is not associated with improved clinical outcomes.[36,37] It has been estimated that more than 65,000 patients are treated in U.S. emergency departments annually for warfarin-related hemorrhage.[32]

The Copenhagen AFASAK Study enrolled 1,007 outpatients with chronic nonrheumatic AF and compared 3 treatment groups: warfarin, aspirin, and placebo.[27] After 2-year follow up, a primary endpoint of a composite of stroke, transient ischemic attack, or embolic complications to peripheral vasculature was significantly lower in the warfarin (1.4%) compared with the aspirin (6.0%) and placebo groups (6.3%). However, there was a significantly higher incidence of nonfatal bleeding complications in the warfarin group (6.3%) compared with aspirin (0.6%) or placebo (0).

The Stroke Prevention in Atrial Fibrillation (SPAF) study directly compared warfarin, aspirin, and placebo in the prevention of stroke in AF patients.[38] It showed that warfarin [relative risk reduction (RRR) = 0.67; 95% (confidence interval) CI: 0.27–0.85; $P = 0.01$] and aspirin (RRR = 0.42; 95% CI: 0.09–0.63; $P = 0.02$) were both effective in reducing ischemic stroke and systemic emboli in patients with AF and warfarin appears to have a stronger effect. This study was terminated early due to achievement of primary efficacy endpoint, however, underpowered due to low number of thromboembolic events.

In the SPAF-II trial, researchers assessed the effectiveness of warfarin (prothrombin time ratio 1.3–1.8) compared to aspirin (325 mg daily) and explored the differential effects of the 2 treatments according to age. The study compared warfarin with aspirin for prevention of ischemic stroke and systemic embolism in 2 parallel randomized trials involving 2 cohorts: age ≤ 75 years (715 patients) versus age > 75 years (385 patients). In the younger subset of patients, warfarin decreased the absolute rate of primary events by 0.7% per

year [relative risk (RR) = 0.67, 95% CI: 0.4–1.7, $P = 0.24$], compared to the older patients in the study, in which warfarin decreased the absolute rate of primary events by 1.2% per year (RR = 0.73, 95% CI: 1.7–4.1, $P = 0.39$). Younger patients without risk factors had a low rate of stroke when treated with aspirin. In older patients, the rate of stroke (ischemic and hemorrhagic) was substantial (4.8% vs 3.6%), irrespective of which agent was given.[10]

Given many studies had shown benefits of warfarin in the prevention of thromboembolic events in AF, monitoring INRs while on warfarin had been studied to find effective ranges of anticoagulation. Studies have indicated the risk of hemorrhage rises rapidly at INR > 4.0–5.0.[39] One study demonstrates the optimum goal for anticoagulant therapy should be to maintain INR between 2.0 and 3.0 compared with INR < 2.0. One study agrees and reports that anticoagulation resulting in an INR of 2.0 or greater reduces both the incidence of ischemic stroke as well as the risk of death from stroke compared to INRs < 1.5 and 1.5–1.9.[40] Similar findings were also seen in the European Atrial Fibrillation Trial Study Group that looked at optimal oral anticoagulant therapy in patients with nonrheumatic AF and recent cerebral ischemia. This trial also concluded that the target value for the INR should be set at 3.0, and values below 2.0 and above 5.0 should be avoided.[41] According to the current guidelines, most patients with AF should maintain an INR of 2.0–3.0 with the exception for an INR of 2.5–3.5 for AF patients with a mechanical valve (other than On-X aortic valve) or requiring a higher INR goal due to thrombophilia.[42]

With knowledge of optimal INR range, trials looked at issues that occur during time outside of therapeutic range. One meta-analysis that included 35 studies from 31 patient cohorts showed the mean TTR was 64%, with a range of 25–90%.[43] It showed increasing mean TTR was significantly associated with a decreased incidence of both major bleeding and stroke/systemic embolism ($P < 0.01$). Another cross-sectional study enrolled 300 nonvalvular AF patients on long-term warfarin with a mean TTR of 47.0%, which showed achieving TTR > 60% did not compromise health-related quality of life and treatment satisfaction.[44]

INR stability, however, can be interrupted when anticoagulation is held for surgery. Bridging anticoagulation is sometimes during anticoagulation interruptions, but is associated with higher risk for bleeding and adverse events.[45] Therefore, bridging should only be used in selected patients with a high risk of thromboembolic events and a low bleeding risk.

ANTIPLATELET THERAPY

The use of aspirin 325 mg daily alone in AF has shown to be inferior to warfarin shown in the SPAF-II study.[46] In the Copenhagen AFASAK study where aspirin 75 mg daily was used, warfarin had significantly lower thromboembolic complications compared with aspirin and placebo.[27] Hence, aspirin is rarely considered as a single agent in the prevention of stroke in AF.

Dual antiplatelet therapy was also studied in stroke prevention. The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE A) trial compared clopidogrel and aspirin to aspirin alone. It showed a trend toward lower major vascular event (stroke, noncentral nervous system embolism, myocardial infarction, or vascular death) was 6.8% with clopidogrel and aspirin versus 7.6% per year (RR = 0.89; 95% CI: 0.81–0.98; $P = 0.01$) with aspirin alone but also increased risk of major hemorrhage (2.0% vs 1.3% per year, RR = 1.57; 95% CI: 1.29–1.92; $P < 0.001$).[47,48]

The clopidogrel plus aspirin versus oral anticoagulation for AF in the Atrial fibrillation clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W) trial further compared patients on clopidogrel (75 mg per day) plus aspirin (75–100 mg daily) to patients on oral anticoagulation therapy (target INR of 2.0–3.0).[47,49] First occurrence of stroke, non-CNS systemic embolism, myocardial infarction, or vascular death was set as the primary outcome. This study, however, was stopped early because of clear evidence of superiority of oral anticoagulation therapy with lower rates of stroke and risk of bleeding (3.93% per year) compared to clopidogrel plus aspirin (5.60%; RR = 1.44, 95% CI: 1.18–1.76; $P = 0.0003$).

DIRECT ORAL ANTICOAGULANTS

DOACs are direct inhibitors of the coagulation cascade involved in the process of generation of a fibrin clot, includes factor Xa inhibitors and direct thrombin (factor IIa) inhibitors (DTI). Factor Xa is a key factor of both the intrinsic and extrinsic coagulation pathways of coagulation cascade. Thrombin is the last enzyme of the coagulation cascade, which converts fibrinogen to fibrin to form thrombus. Direct factor Xa inhibitors bind to the activation site of factor Xa and prevent factor Xa from activating prothrombin to thrombin (factor IIa), while DTI directly inhibits the conversion. Ximelagatran was the first DOAC approved world-wide (in Germany, Portugal, Sweden, Finland, Norway, Iceland, Austria, Denmark, France, Switzerland, Argentina, and Brazil). However, it was never approved in the U.S. and discontinued distribution in approved countries after reports of hepatotoxicity in 2006.[50] Currently, the U.S. Food and Drug Administration (FDA) approved oral factor Xa inhibitors include rivaroxaban, apixaban, edoxaban, and betrixaban, while the only oral DTI is dabigatran.

The use of DOACs has been increasing in recent years. Unlike warfarin, DOACs do not require frequent monitoring of the patient's INR. In addition, there are no food interactions and fewer drug interactions with DOACs. By 2016, the prescription of DOACs had exceeded warfarin for AF patients.[51] Several meta-analyses and systematic reviews showed superiority with DOACs over VKA in patients with AF. In one meta-analysis that included the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY), the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF), Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE), and Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE-TIMI 48) trials, DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) were compared with warfarin. DOACs were associated with a significant reduction of embolic stroke/systemic embolism [RRR= 13.7%, absolute risk reduction (ARR) = 0.78%, number needed to treat (NNT) = 127], hemorrhagic stroke (RRR = 50.0%, ARR = 0.63%, NNT = 157), intracranial hemorrhage (RRR = 46.1%, ARR = 0.88%, NNT = 113), and major bleeding (RRR = 10.6%, ARR = 0.68%, NNT = 147).[52] Another systematic review that included 6 randomized studies showed DOACs were associated with lower all-cause mortality (RR = 0.88, 95% CI: 0.82–0.96), fatal bleeding (RR = 0.60, 95% CI: 0.46–0.77), but had higher discontinuation rates due to adverse events (RR = 1.23, 95% CI: 1.05–1.44).[53] Another meta-analysis of 12 phase II and phase III randomized control trials (RCTs) with 54,875 AF patients showed DOACs compared to warfarin had significantly lower all-cause mortality (RR = 0.89; 95% CI: 0.83–0.96), cardiovascular mortality (RR = 0.89; 95% CI: 0.82–0.98), and stroke/systemic embolism (RR = 0.77; 95% CI: 0.70–0.86), as well as major bleeding (RR = 0.86; 95% CI: 0.72–1.02) and intracranial hemorrhage (RR = 0.46; 95% CI: 0.39–0.56).[54] Multiple other meta-analyses also showed more favorable clinical outcomes with DOACs compared to VKA in patients with nonvalvular AF.[55–57] A summarization of RCTs of DOAC versus warfarin in nonvalvular AF is provided in Table 2.

TABLE 2. Summary of the Major Randomized Trials Evaluating Direct Oral Anticoagulants in Atrial Fibrillation

Trial Acronym	N	DOAC	Mean $CHADS_2$	Mean Percent Time in INR Range	Death	Stroke or System Embolic Events	Hemorrhagic Stroke	Major Bleeding
RE-LY*	18,113	Dabigatran 110 mg twice daily	2.1	64%	RR 0.91 (0.8–1.03)	RR 0.91 (0.74–1.11)	RR 0.31 (0.17–0.56)	RR 0.80 (0.69–0.93)
		Dabigatran 150 mg twice daily			RR 0.88 (0.77–1.00)	RR 0.66 (0.53–0.82)	RR 0.26 (0.14–0.49)	RR 0.93 (0.81–1.07)
ROCKET-AF*	14,264	Rivaroxaban 20 mg once daily	3.5	55%	HR 0.92 (0.82–1.03)	HR 0.88 (0.75–1.03)	HR 0.59 (0.37–0.93)	HR 1.04 (0.9–1.2)
ARISTOTLE*	18,201	Apixaban 5 mg twice daily	2.1	62%	HR 0.89 (0.80–0.998)	HR 0.79 (0.66–0.95)	HR 0.51 (0.35–0.75)	HR 0.69 (0.6–0.8)
ENGAGE AF-TIMI 48*	21,105	Edoxaban 30 mg once daily	2.8	65%	HR 0.87 (0.79–0.96)	HR 1.13 (0.96–1.34)	HR 0.33 (0.22–0.50)	HR 0.47 (0.41–0.55)
		Edoxaban 60 mg once daily			RR 0.90 (0.85–0.95)	HR 0.87 (0.73–1.04)	HR 0.54 (0.38–0.77)	HR 0.80 (0.71–0.91)

$CHADS_2$, score to estimate risk of stroke with 1 point assigned for each of the following: history of congestive heart failure, hypertension, age ≥75 years, or diabetes, and 2 points assigned for prior stroke or transient ischemic attack; DOAC, direct oral anticoagulant; HR, hazard ratio; INR, international normalized ratio; N, Number of patients enrolled; RR, relative risk.

*All 4 trials were compared to warfarin (target INR 2.0–3.0).

DABIGATRAN

Dabigatran was the first FDA-approved DOAC for AF in 2010. The RE-LY trial was an open label, noninferiority RCT designed to compare 2 doses of dabigatran (110 mg twice daily and 150 mg twice daily) with warfarin in patients who had AF and were at increased risk for stroke ($CHADS_2$ score > 1). A total of 18,113 patients were enrolled from 44 countries. The primary efficacy outcome was embolic stroke or systemic embolism, which showed similar rates in patients receiving 110 mg of dabigatran twice daily (RR = 0.91; 95% CI: 0.74–1.11; $P < 0.001$ for noninferiority) and lower rates in patients receiving 150 mg of dabigatran twice daily (RR 0.66; 95% CI: 0.53–0.82; $P < 0.001$ for superiority). The primary safety outcome was major hemorrhage, which was lowest in 110 mg dabigatran group (2.71% per year, $P = 0.003$) and similar between warfarin (3.36% per year) and the 150 mg dabigatran group (3.11% per year, $P = 0.31$). The annual rate of hemorrhagic stroke in the 150 mg dabigatran group (0.10%, $P < 0.001$) and the 110 mg dabigatran group (0.12%, $P < 0.001$) were both significantly lower than warfarin (0.38%). Mortality rates were similar between groups (warfarin, 4.13%; 110 mg dabigatran, 3.75%, $P = 0.13$; 150 mg dabigatran, 3.64%, $P = 0.051$).[13] This trial prompted the approval of dabigatran by FDA (at doses of 150 mg and 75 mg twice daily) and in the European Union.

The Long-term Multicenter Extension of Dabigatran Treatment in Patients with Atrial Fibrillation (RELY-ABLE) trial, which is an observational extension of the RE-LY trial, showed similar efficacy of preventing embolic stroke and mortality rates but lower risk of bleeding in 110 mg versus 150 mg of dabigatran.[58]

RIVAROXABAN

Rivaroxaban was approved by the FDA in 2011 and was the first oral factor Xa inhibitor approved for stroke prevention in nonvalvular AF. The ROCKET-AF study was a randomized, double-blinded trial that recruited 14,264 patients receiving either rivaroxaban (20 mg/day or 15 mg/day with decreased kidney function) or dose-adjusted warfarin from 1,178 participating sites in 45 countries.[15] The primary efficacy endpoint was the composite of stroke (ischemic or hemorrhagic) and systemic embolism. Rivaroxaban (1.7%) was noninferior [hazard ratio (HR) = 0.79, 95% CI: 0.66–0.96; $P < 0.001$ for noninferiority] to warfarin (2.2%). In the intention-to-treat analysis, rivaroxaban (2.1%) was noninferior to, but not superior to, warfarin (2.4%, HR = 0.88; 95% CI: 0.74–1.03; $P < 0.001$ for noninferiority; $P = 0.12$ for superiority) with respect to the primary efficacy endpoint. The primary safety endpoint of the trial was a composite of major and nonmajor clinically relevant bleeding events. Primary safety endpoint was met in similar rates in the rivaroxaban group (14.9%) and in the warfarin group (14.5%, HR = 1.03; 95% CI: 0.96–1.11; $P = 0.44$). Of note, intracranial hemorrhage (0.5% vs 0.7%, $P = 0.02$) and fatal bleeding (0.2% vs 0.5%, $P = 0.003$) were both significantly lower in rivaroxaban compared to warfarin.[15]

Another randomized trial was performed in Japan to establish the efficacy of lower dose of rivaxoraban (15 mg once daily) in the Japanese population.[59] The J-ROCKET AF trial was a phase III randomized double-blind trial, which included 1,280 patients with nonvalvular AF randomized to 15 mg once daily rivaroxaban or dose-adjusted warfarin. Rivaroxaban was noninferior to warfarin in a composite of stroke and systemic embolism with a strong trend favoring rivaroxaban (HR 0.49, 95% CI: 0.24–1.00; $P = 0.05$). Rivaroxaban was also noninferior in a composite of major bleeding and nonmajor clinically relevant bleeding rivaroxaban (HR 1.11, 95% CI: 0.87–1.42, $P < 0.001$).

APIXABAN

Apixaban was approved in 2012, and was the second factor Xa inhibitor approved by the FDA. The Apixaban versus Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial studied the efficacy of apixaban in nonvalvular AF patients unsuitable for VKA.[60] It was a multicenter, double-blind, randomized, placebo-controlled trial that compared apixaban with aspirin. A total of 5,599 patients were enrolled; 2,808 were randomized to the apixaban group (apixaban 5 mg twice daily plus placebo) (or apixaban 2.5 mg twice daily if they met at least 2 of the following criteria: age ≥ 80 years, weight ≤ 60 kg, or creatinine ≥ 1.5 mg/dL) while 2,791 were randomized to the aspirin group (81–325 mg daily plus placebo). Stroke and/or systemic embolism was lower with apixaban (1.6% annually) compared to aspirin (3.7%, HR 0.45; 95% CI: 0.32–0.62; $P < 0.001$), while there was no difference in major bleeding (1.4% vs 1.2%, HR 1.13; 95% CI: 0.74–1.75; $P = 0.57$).

The ARISTOTLE trial enrolled 18,201 patients with AF with additional risk factor for stroke and compared apixaban (5 mg twice daily or 2.5 mg twice daily if patients met criteria similar to

AVERROES trial, above) with warfarin (target INR 2.0–3.0).[14] Apixaban was associated with lower rates of stroke and systemic embolism compared to warfarin (1.27% vs 1.60% per year, respectively; HR 0.79; 95% CI: 0.66–0.95; $P < 0.001$ for noninferiority; $P = 0.01$ for superiority). Major bleeding was lower with apixaban compared to warfarin (2.13% vs 3.09% per year, respectively; HR 0.69; 95% CI: 0.60–0.80; $P < 0.001$). Mortality was similar with apixaban and warfarin (3.52% vs 3.94% per year, respectively; HR 0.89; 95% CI: 0.80–0.99; $P = 0.047$).

The Aspirin Placebo in Patients with Atrial Fibrillation and ACS or PCI (AUGUSTUS) was an open-label trial, which compared the efficacy of apixaban with VKA with or without the addition of aspirin to a P2Y12 inhibitor, in patients with indications for dual antiplatelet therapy (DAPT) in the setting of acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI).[61] Because of its 2×2 design, apixaban was able to be compared with VKA directly. Compared to warfarin (14.7%), apixaban (10.5%) was associated with less major or clinically relevant nonmajor bleeding (HR = 0.69, 95% CI: 0.58–0.81, $P < 0.001$ for both noninferiority and superiority). The mortality rate (3.3% vs 3.2%, HR 1.03, 95% CI: 0.75–1.42) was similar, while the rate of stroke was lower with apixaban (0.6% vs 1.1%, HR 0.50, 95% CI: 0.26–0.97).

EDOXABAN

Edoxaban was the latest factor Xa inhibitor approved by the FDA in 2015. The ENGAGE AF-TIMI 48 trial was a 3-group RCT comparing high-dose (60 mg daily) and low-dose (30 mg daily) edoxaban with warfarin in the prevention of stroke or systemic embolism.[62] A previous phase 2 RCT established the safety of daily edoxaban doses.[63] A total of 21,105 patients with nonvalvular AF and $CHADS_2$ score > 2 were enrolled; the median follow-up was 2.8 years. The primary efficacy endpoint was a composite of stroke and systemic embolism. The primary safety endpoint was major bleeding. Both low-dose (1.61% annually; HR 1.07; 97.5% CI: 0.87–1.31; $P = 0.005$ for noninferiority) and high-dose edoxaban (1.18%; HR 0.79; 97.5% CI: 0.63–0.99; $P < 0.001$ for noninferiority) were noninferior in preventing stroke or systemic embolism when compared with warfarin (1.50%, median time in the therapeutic range of 68.4%). In the intention-to-treat analysis for the primary efficacy endpoint, there was a trend favoring high-dose edoxaban versus warfarin (HR 0.87; 97.5% CI: 0.73–1.04; $P = 0.08$) and an unfavorable trend with low-dose edoxaban versus warfarin (HR 1.13; 97.5% CI: 0.96–1.34; $P = 0.10$). Regarding major bleeding, both high-dose edoxaban (2.75% annually; HR 0.80; 95% CI: 0.71–0.91; $P < 0.001$) and low-dose edoxaban (1.61%; HR 0.47; 95% CI: 0.41–0.55; $P < 0.001$) had lower rates compared with warfarin (3.43%). All-cause mortality was also lower with both high-dose (3.99% annually, $P = 0.004$) and low-dose (3.80%, $P << 0.001$) edoxaban compared with warfarin (4.35%).

COMPARISON OF DOACS

There have been no RCTs that have made head-to-head comparisons between different DOACs. However, the efficacy, cost effectiveness, and safety of different DOACs were compared in a systematic review and network analysis that analyzed 23 phase II and phase III RCTs involving a total of 94,656 patients.[64] DOACs included in the analysis were apixaban, edoxaban, rivaroxaban, and dabigatran. Among the 23 studies included, 13 were comparing DOAC with warfarin. Network meta-analysis showed dabigatran 150 mg twice daily had a lower risk of stroke or systemic embolism compared with edoxaban 60 mg once daily [odds ratio (OR) = 1.33, 95% CI: 1.02–1.75] and rivaroxban 20 mg once daily (OR = 1.35, 95% CI: 1.03–1.78) but similar to apixaban 5 mg twice daily (OR = 0.82, 95% CI: 0.62–1.08). As for major bleeding risk, apixaban was similar to edoxaban (OR = 1.11, 95% CI: 0.92–1.35) and was lower compared to dabigatran (OR = 1.33, 95% CI: 1.09–1.62) and rivaroxaban (OR = 1.45, 95% CI: 1.19–1.78). Clinically relevant bleeding was similar in apixaban and dabigatran with trend favoring apixaban (OR = 2.32, 95% CI: 0.74–8.63), but higher in edoxaban (OR = 1.24, 95% CI: 1.09–1.42) and rivaroxaban (OR = 1.53, 95% CI: 1.33–1.75).

REVERSAL AGENTS OF DOACS

Initially, the lack of reversal agents for DOACs had been one disadvantage when compared with VKA. Idarucizumab was approved by the FDA as the first reversal agent for DOACs.[65] It is a monoclonal antibody for dabigatran and does not reverse other DOACs. Andexanet alfa is a recombinant modified version of human activated factor X and it was approved as a reversal agent for both rivaroxaban and apixaban by the FDA in 2018.[66] Of note, there are no RCTs that studied the efficacy of andexanet alfa to date; the earliest RCT result is not expected until 2023.[67] Ciraparantag is a universal reversal agent for factor Xa inhibitors, dabigatran, and heparin by binding anticoagulants via hydrogen bonds and charge-charge interactions.[68] It is under Fast Track Review by the FDA but has not yet been approved.

SPECIAL CONSIDERATION

Valvular Heart Disease and Prosthetic Valves

Currently, the antithrombotic treatment in AF patients with valvular heart disease (VHD) or bioprosthetic valves remains controversial, and the optimal treatment for these conditions is still under investigation.[69,70] Several meta-analyses demonstrated that in AF patients with VHD, edoxaban, dabigatran, and apixaban exhibited similar efficacy, and similar or reduced risks of stroke or systemic embolism as well as bleeding, compared to warfarin.[71–73] However, rivaroxaban was associated with increased major bleeding, but not intracranial hemorrhage or mortality rate.[15,74] In AF patients with bioprosthetic heart valves, the comparison between DOACs versus warfarin showed that DOACs are noninferior to warfarin with respect to safety and efficacy.[72,75,76] In the ENGAGE AF-TIMI 48 trial, AF patients with bioprosthetic heart valves treated with 60 mg edoxaban had similar rates of stroke or systemic embolism and major bleeding compared with warfarin, while those treated with 30 mg edoxaban had similar rates of stroke or systemic embolism but lower rates of major bleeding.[75] In the ARISTOTLE trial, in AF patients with bioprosthetic heart valves, apixaban 5 mg twice daily was noninferior to VKA with respect to stroke or systemic embolism, and major bleeding.[76] Nonetheless, these comparisons between AF patients with bioprosthetic heart valves were based on a very small subgroup of randomized patients. In a recent RCT comparing rivaroxaban versus warfarin in patients with AF and a bioprosthetic mitral valve (RIVER trial, NCT02303795), rivaroxaban 20 mg once daily was noninferior to dose-adjusted warfarin in the mean time until the primary outcome event (consisting of a composite of death and major cardiovascular events including stroke, transient ischemic attack, systemic embolism, valve thrombosis, or hospitalization for heart failure; 347.5 vs 340.1 days, respectively; 95% CI: −1.4 to 16.3; $P < 0.001$ for noninferiority) as well as for major bleeding (1.4% vs 2.6%, respectively; HR = 0.54, 95% CI: 0.21–1.35).[77] Furthermore, an ongoing observational study is being conducted in Japan to compare DOACs versus warfarin versus antiplatelet therapy in AF patients with bioprosthetic valves.[78] The Investigation of Rheumatic AF Treatment Using Vitamin K Antagonists, Rivaroxaban or Aspirin Studies (INVICTUS-VKA) trial is an international, multicenter, open-label, phase III RCT, planning to enroll more than 20,000 patients, comparing rivaroxaban 20 mg with VKAs for the prevention of stroke or systemic

embolism in AF patients with rheumatic valvular heart disease.[79] The earliest results of INVICTUS-VKA trial are expected to be available in late 2022.

For patients with mechanical heart valves, DOACs should not be used based on current evidence and dabigatran is contraindicated. In the Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement (RE-ALIGN) trial, dabigatran (dosed adjusted based on trough plasma level) compared to warfarin (INR target of 2–3 or 2.5–3.5, depending upon thromboembolic risk factors) showed an increased risk of ischemic or unspecified stroke (5% vs 0), myocardial infarction (3% vs 0), valve thrombosis without symptoms (3% vs 0), as well as major bleeding (4% vs 2%, pericardial bleeding in all the cases), in patients who had undergone aortic- or mitral-valve replacement within the past 7 days and those who had undergone such replacement at least 3 months earlier.[80] The trial was stopped early because of excess of thromboembolic and bleeding events in the dabigatran group after 252 patients. This prompts the FDA to release a safety announcement that dabigatran should not be used in patients with mechanical prosthetic heart valves.[81] The RIWA trial was a proof-of-concept, open-label, RCT that recruited a total of 72 patients to compare the incidence of thromboembolic and bleeding events in patients with mechanical heart valves taking rivaroxaban (15 mg twice daily) and dose-adjusted warfarin.[82] During a 90 days follow-up period, rivaroxaban and warfarin had a similar rate of a composite primary efficacy outcome of stroke, transient ischemic attack, silent brain infarction, and systemic embolism (4.3% vs 14.3%, RR = 0.27, 95% CI: 0.02–2.85; $P = 0.25$). No case of major bleeding, intracranial hemorrhage, fatal bleeding, and clinically relevant nonmajor bleeding were not reported in either groups during the follow-up period. However, the RIWA trial was only a single-center pilot study with small sample size and short follow-up and needs to be confirmed with multicenter RCTs. Randomized trials of apixaban or edoxaban have not been completed in patients with mechanical valves. The PROACT Xa trial is an open-label, RCT to compare apixaban with warfarin in patients with an On-X Aortic Heart Valve or On-X Ascending Aortic Prosthesis with the Vascutek Gelweave Valsalva Graft, started in 2020 and estimated to be completed in 2024 with a target sample size of 1,000 patients.[83]

Compromised Kidney Function

In AF patients with CKD, warfarin use was associated with increased risk of hemorrhagic stroke but associated with no change in the incidence of ischemic stroke.[84] In contrast, dose-adjusted apixaban have shown to reduce the risks of bleeding, thromboembolism, and death compared to warfarin, and it is currently the only DOAC approved to be used in patients with end-stage renal disease.[85,86] Notably, dabigatran, rivaroxaban, and edoxaban should be avoided in patients with end-stage renal disease or on dialysis, although each has a different cut-off for glomerular filtration rate.[18]

Concomitant Use of Antiplatelet Agents

In AF patients with ACS or PCI classically requiring DAPT as well as anticoagulation, the AUGUSTUS trial showed that with the addition of aspirin to a P2Y12 inhibitor resulted in more major and clinically relevant bleeding (16.1% vs 9.0%, HR 1.89, 95% CI: 1.59–2.24, $P < 0.001$), regardless of whether warfarin or apixaban was used for anticoagulation, without an improvement of death or hospitalization rate (26.2% vs 24.7%, HR = 1.08, 95% CI: 0.96–1.21, P = nonsignificant) or rate of stroke (0.9% vs 0.8%, HR = 1.06, 95% CI: 0.98–1.98).[61] Therefore, the American College of Cardiology recommends against combined use of DAPT with anticoagulation in general and only if it is necessary, a short duration (less than 30 days) of combined use is recommended.[87]

In AF patients with stable coronary artery disease, the Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease (AFIRE) trial showed that rivaroxaban monotherapy was noninferior to combination therapy with rivaroxaban plus a single antiplatelet agent in a composite efficacy endpoint of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or death from any cause (HR = 0.72, 95% CI: 0.55–0.95, $P < 0.001$ for noninferiority). At the same time, rivaroxaban monotherapy was superior to combination therapy in major bleeding (HR = 0.59, 95% CI: 0.39–0.89, $P = 0.01$ for superiority). The trial was stopped early due to increased mortality in the combination therapy group.[88]

In elderly AF patients, one study included patients ≥90 years of age and showed DOACs (dabigatran, rivaroxaban, and apixaban) and warfarin were similarly effective in preventing stroke or thromboembolic events (4.07% vs 4.59%, respectively; HR = 1.16, 95% CI: 0.61–2.22, $P = 0.654$), but a reduced risk of intracranial hemorrhage (0.42% vs 1.63%, respectively; HR = 0.32, 95% CI: 0.10–0.97, $P = 0.044$).[89] Another cohort study compared clinical outcomes by frailty in Medicare patients (patients aged over 65 or with disability) with AF using warfarin vs DOACs. Compared to warfarin, apixaban was associated with lower rates of adverse events (defined as a composite of death, ischemic stroke, or major bleeding) across all frailty levels, while dabigatran and rivaroxaban only had lower event rates with nonfrail patients.[90]

Periprocedural Management

Two meta-analyses and 3 RCTs showed in AF patients undergoing AF ablation, comparing with uninterrupted warfarin, continuous DOACs were associated with similar or lower incidence of periprocedural thromboembolic events and reduced major bleeding.[91–95] In the Role of Coumadin in Preventing Thromboembolism in AF Patients Undergoing Catheter Ablation (COMPARE) trial, interrupted warfarin (2–3 days prior to ablation) with bridging of low-molecular-weight heparin was associated with a higher periprocedural risk of thromboembolic events (4.9% vs 0.25%, $P > 0.001$) and a similar bleeding complication rate (0.76% vs 0.38, $P = 0.31$).[96] However, in the ABlation peRIoperative DabiGatran in use Envisioning in Japan (ABRIDGE-J) trial, minimally interrupted dabigatran before catheter ablation (holding of 1–2 doses) exhibited similar thromboembolic risk (0% vs 0.5%) and reduced bleeding complications (1.4% vs 5.0%, $P = 0.03$) compared to uninterrupted warfarin.[97] In one Korean multicenter RCT, short interruption of DOACs (procedure day single-dose skipped or 24-hour skipped) compared with uninterrupted DOACs before AF ablation had a comparable efficacy in the prevention of thromboembolic event (no event reported in all 3 groups) and similar bleeding risk ($P > 0.05$), regardless of the type of DOACs used.[98] Base on the aforementioned findings, current consensus recommend uninterrupted anticoagulation or minimally interrupted DOACs prior to ablation. Immediately postablation, anticoagulation should be continued for at least 2 months and further continuation should depend on patient's risk for thromboembolism.[99] Some studies suggest that it may be safe to discontinue anticoagulants (warfarin or DOACs) in postablation patients under close monitoring; however, it is debatable in real-world practice.[100,101]

In AF patients treated with warfarin receiving elective procedures, the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) trial showed increased incidence of myocardial infarction, stroke or systemic embolism, major bleeding, hospitalization, and death within 30 days in patients receiving bridging compared to no bridging.[102] The Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation (BRIDGE) trial also showed forgoing bridging was noninferior to perioperative bridging with low-molecular-weight heparin in perspective of

thromboembolic prevention. Moreover, no-bridging group exhibited significantly decreased incidence of major bleeding compared to bridging group.[103] Similarly, an observational study comparing heparin bridging versus no bridging in patients receiving DOACs, including rivaroxaban, dabigatran, and apixaban, showed no significant difference in cardiovascular events, while bridging led to increased major bleeding complications.[104] Therefore, bridging in routine prophylactic anticoagulation in AF in general should be avoided with the exception of presence of a mechanical mitral valve, previous thromboembolism during interruption of chronic anticoagulation, embolic stroke/thromboembolic events within previous 3 months, or a very high stroke risk ($CHADS_2$ score of 5 or 6).[105]

Patients With Contraindication to Anticoagulation

In patients with unacceptably high risk of bleeding with anticoagulation, left atrial appendage (LAA) occlusion devices/procedures are considered to prevent embolic stroke in AF patients. For AF patients undergoing cardiac surgery with an indication long-term anticoagulation but also a contraindication, studies showed surgical LAA occlusion was associated with a reduced risk of ischemic stroke or systemic embolic and mortality.[106,107] Percutaneous LAA closure devices including the Watchman and Amplatzer devices are approved by the FDA. The LARIAT system has also been used; importantly, this system is approved by the FDA for soft tissue closure/approximation only, and not specifically for prevention of thromboembolism with LAA occlusion. In the percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation (PROTECT AF) and the Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy (PREVAIL) trial, the Watchman device was noninferior to warfarin in the prevention of stroke, systemic embolism, or death.[108,109] In the Amplatzer Amulet Left Atrial Appendage Occluder Versus Watchman Device for Stroke Prophylaxis (Amulet IDE) trial, the Amplatzer Amulet device was noninferior for safety and effectiveness of stroke prevention to the WATCHMAN device and had a higher LAA occlusion rate.[110] The WaveCrest device is approved by European Union CE but has not yet received FDA approval. The WAveCrest Vs. Watchman TranssEptal LAA Closure to REduce AF-Mediated STroke 2 (WAVECREST2, NCT03302494) trial is an ongoing phase 3 RCT aimed to compare the safety and effectiveness of WaveCrest LAA Occlusion system with Watchman.[111]

REFERENCES

1. Wolf PA, Benjamin EJ, Belanger AJ, et al. Secular trends in the prevalence of atrial fibrillation: The Framingham Study. *Am Heart J*. Apr 1996;131:790–795.
2. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation*. Jan 21 2014;129:e28–e292.
3. Kim MH, Johnston SS, Chu BC, et al. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. *Circ Cardiovasc Qual Outcomes*. 2011;4:313–320.
4. Kannel WB, Wolf PA, Benjamin EJ, et al. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol*. 1998;82:2n–9n.
5. Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation*. Jun 17 2003;107:2920–2925.
6. Krahn AD, Manfreda J, Tate RB, et al. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. *Am J Med*. May 1995;98:476–484.
7. Stewart S, Hart CL, Hole DJ, et al. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med*. Oct 1 2002;113:359–364.
8. Ott A, Breteler MM, de Bruyne MC, et al. Atrial fibrillation and dementia in a population-based study. The Rotterdam Study. *Stroke*. Feb 1997; 28:316–321.
9. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014;64:e1–e76.
10. Hart RG, Pearce LA, McBride R, et al. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF I-III clinical trials. The Stroke Prevention in Atrial Fibrillation (SPAF) Investigators. *Stroke*. Jun 1999;30:1223–1229.
11. Go AS, Hylek EM, Chang Y, et al. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? *JAMA*. Nov 26 2003;290:2685–2692.
12. Ahrens I, Lip GY, Peter K. New oral anticoagulant drugs in cardiovascular disease. *Thromb Haemost*. Jul 2010;104:49–60.
13. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. Sep 17 2009;361:1139–1151.
14. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. Sep 15 2011;365:981–992.
15. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. Sep 8 2011;365:883–891.
16. Pisters R, Nieuwlaat R, Lane DA, et al. Potential net clinical benefit of population-wide implementation of apixaban and dabigatran among European patients with atrial fibrillation. A modelling analysis from the Euro Heart Survey. *Thromb Haemost*. Feb 2013;109:328–336.
17. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association practical guide on the use of non-vitamin-K antagonist anticoagulants in patients with non-valvular atrial fibrillation: executive summary. *Eur Heart J*. Jul 14 2017;38:2137–2149.
18. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the heart rhythm society in collaboration with the society of thoracic surgeons. *Circulation*. Jul 9 2019;140:e125–e151.
19. Andrade JG, Aguilar M, Atzema C, et al. The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm society comprehensive guidelines for the management of atrial fibrillation. *Can J Cardiol*. Dec 2020;36:1847–1948.
20. Van Staa TP, Setakis E, Di Tanna GL, et al. A comparison of risk stratification schemes for stroke in 79,884 atrial fibrillation patients in general practice. *J Thromb Haemost*. Jan 2011;9:39–48.
21. Kabra R, Girotra S, Vaughan Sarrazin M. Refining stroke prediction in atrial fibrillation patients by addition of African-American Ethnicity to CHA2DS2-VASc Score. *J Am Coll Cardiol*. Aug 2 2016;68:461–470.
22. Piccini JP, Stevens SR, Chang Y, et al. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R(2)CHADS(2) index in the 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) and ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) study cohorts. *Circulation*. Jan 15 2013;127:224–232.
23. Singer DE, Chang Y, Borowsky LH, et al. A new risk scheme to predict ischemic stroke and other thromboembolism in atrial fibrillation: the ATRIA study stroke risk score. *J Am Heart Assoc*. Jun 21 2013;2:e000250.
24. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J*. 2012;33:1500–1510.
25. Roldán V, Marín F, Manzano-Fernández S, et al. The HAS-BLED score has better prediction accuracy for major bleeding than CHADS2 or CHA2DS2-VASc scores in anticoagulated patients with atrial fibrillation. *J Am Coll Cardiol*. Dec 10 2013;62:2199–2204.
26. Mtwesi V, Amit G. Stroke prevention in atrial fibrillation: the role of oral anticoagulation. *Med Clin North Am*. Sep 2019;103:847–862.
27. Petersen P, Boysen G, Godtfredsen J, et al. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. *Lancet*. Jan 28 1989;1:175–179.
28. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med*. Jul 11 1994;154:1449–1457.
29. Ezekowitz MD, Bridgers SL, James KE, et al. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. *N Engl J Med*. Nov 12 1992;327:1406–1412.
30. Oldenburg J, Watzka M, Rost S, et al. VKORC1: molecular target of coumarins. *J Thromb Haemost*. Jul 2007;5:1–6.

31. Kaminsky LS, Zhang ZY. Human P450 metabolism of warfarin. *Pharmacol Ther*. 1997;73:67–74.
32. Harter K, Levine M, Henderson SO. Anticoagulation drug therapy: a review. *West J Emerg Med*. Jan 2015;16:11–17.
33. Connolly SJ, Laupacis A, Gent M, et al. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. *J Am Coll Cardiol*. Aug 1991;18:349–355.
34. van Walraven C, Hart RG, Singer DE, et al. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. *JAMA*. Nov 20 2002;288:2441–2448.
35. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. Feb 2010;137:263–272.
36. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. Dec 2 2014;64:e1–76.
37. Nguyen NY, Frishman WH. Restarting oral anticoagulation in patients with atrial fibrillation after an intracranial hemorrhage. *Cardiol Rev*. 2020;28:190–196.
38. Stroke prevention in atrial fibrillation study. Final results. *Circulation*. Aug 1991;84:527–539.
39. Hylek EM, Skates SJ, Sheehan MA, et al. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. *N Engl J Med*. Aug 22 1996;335:540–546.
40. Hylek EM, Go AS, Chang Y, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med*. Sep 11 2003;349:1019–1026.
41. Optimal oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and recent cerebral ischemia. . *N Engl J Med*. 1995;333:5–10.
42. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021;143:e72–e227.
43. Vestergaard AS, Skjoth F, Larsen TB, et al. The importance of mean time in therapeutic range for complication rates in warfarin therapy of patients with atrial fibrillation: a systematic review and meta-regression analysis. *PLoS One*. 2017;12:e0188482.
44. Ng DL, Malik N, Chai CS, et al. Time in therapeutic range, quality of life and treatment satisfaction of patients on long-term warfarin for non-valvular atrial fibrillation: a cross-sectional study. *Health Qual Life Outcomes*. 2020;18:347.
45. Pokorney SD, Simon DN, Thomas L, et al. Patients' time in therapeutic range on warfarin among US patients with atrial fibrillation: results from ORBIT-AF registry. *Am Heart J*. 2015;170:141–8, 148.e1.
46. Stroke Prevention in Atrial Fibrillation Investigators. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. *Lancet*. Mar 19 1994;343:687–691.
47. Connolly SJ, Eikelboom JW, Ng J, et al. Net clinical benefit of adding clopidogrel to aspirin therapy in patients with atrial fibrillation for whom vitamin K antagonists are unsuitable. *Ann Intern Med*. Nov 1 2011;155:579–586.
48. Connolly SJ, Pogue J, Hart RG, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med*. May 14 2009;360:2066–2078.
49. Investigators AWGA, Connolly S, Pogue J, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet*. Jun 10 2006;367:1903–1912.
50. Keisu M, Andersson TB. Drug-induced liver injury in humans: the case of ximelagatran. *Handb Exp Pharmacol*. 2010:407–418.
51. Barnes GD, Lucas E, Alexander GC, et al. National trends in ambulatory oral anticoagulant use. *Am J Med*. Dec 2015;128:1300–5.e2.
52. Ntaios G, Papavasileiou V, Diener HC, et al. Nonvitamin-K-antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and previous stroke or transient ischemic attack: an updated systematic review and meta-analysis of randomized controlled trials. *Int J Stroke*. Aug 2017;12:589–596.
53. Adam SS, McDuffie JR, Ortel TL, et al. Comparative effectiveness of warfarin and new oral anticoagulants for the management of atrial fibrillation and venous thromboembolism: a systematic review. *Ann Intern Med*. Dec 4 2012;157:796–807.
54. Dentali F, Riva N, Crowther M, et al. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. *Circulation*. Nov 13 2012;126:2381–2391.
55. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383:955–962.
56. Bruins Slot KM, Berge E. Factor Xa inhibitors versus vitamin K antagonists for preventing cerebral or systemic embolism in patients with atrial fibrillation. *Cochrane Database Syst Rev*. 2013:Cd008980.
57. Salazar CA, del Aguila D, Cordova EG. Direct thrombin inhibitors versus vitamin K antagonists for preventing cerebral or systemic embolism in people with non-valvular atrial fibrillation. *Cochrane Database Syst Rev*. 2014:Cd009893.
58. Connolly SJ, Wallentin L, Ezekowitz MD, et al. The long-term multicenter observational study of dabigatran treatment in patients with atrial fibrillation (RELY-ABLE) study. *Circulation*. Jul 16 2013;128:237–243.
59. Hori M, Matsumoto M, Tanahashi N, et al. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation – the J-ROCKET AF study –. *Circ J Off J Japan Circ Soc*. 2012;76:2104–2111.
60. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med*. Mar 3 2011;364:806–817.
61. Lopes RD, Heizer G, Aronson R, et al. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *N Engl J Med*. Apr 18 2019;380:1509–1524.
62. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. Nov 28 2013;369:2093–2104.
63. Weitz JI, Connolly SJ, Patel I, et al. Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation. *Thromb Haemost*. Sep 2010;104:633–641.
64. López-López JA, Sterne JAC, Thom HHZ, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review. Network meta-analysis, and cost effectiveness analysis. *BMJ*. 2017;359:j5058.
65. Pollack CV, Jr., Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med*. Aug 6 2015;373:511–520.
66. Connolly SJ, Crowther M, Eikelboom JW, et al. Full study report of andexanet alfa for bleeding associated with factor XA inhibitors. *N Engl J Med*. 2019;380:1326–1335.
67. https://clinicaltrials.gov/ct2/show/NCT03661528
68. Ansell JE, Bakhru SH, Laulicht BE, et al. Single-dose ciraparantag safely and completely reverses anticoagulant effects of edoxaban. *Thromb Haemost*. Jan 26 2017;117:238–245.
69. Hernández Madrid A, Potpara TS, Dagres N, et al. Differences in attitude, education, and knowledge about oral anticoagulation therapy among patients with atrial fibrillation in Europe: result of a self-assessment patient survey conducted by the European Heart Rhythm Association. *Europace*. Mar 2016;18:463–467.
70. Lip GYH, Collet JP, Caterina R, et al. Antithrombotic therapy in atrial fibrillation associated with valvular heart disease: a joint consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology Working Group on Thrombosis, endorsed by the ESC Working Group on Valvular Heart Disease, Cardiac Arrhythmia Society of Southern Africa (CASSA), Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), South African Heart (SA Heart) Association and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE). *Europace*. 2017;19:1757–1758.
71. Pan KL, Singer DE, Ovbiagele B, et al. Effects of non-vitamin K antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and valvular heart disease: a systematic review and meta-analysis. *J Am Heart Assoc*. 2017;6.
72. Malik AH, Yandrapalli S, Aronow WS, et al. Oral anticoagulants in atrial fibrillation with valvular heart disease and bioprosthetic heart valves. *Heart*. Sep 2019;105:1432–1436.
73. Renda G, Ricci F, Giugliano RP, et al. Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and valvular heart disease. *J Am Coll Cardiol*. Mar 21 2017;69:1363–1371.
74. Breithardt G, Baumgartner H, Berkowitz SD, et al. Clinical characteristics and outcomes with rivaroxaban vs. warfarin in patients with non-valvular atrial fibrillation but underlying native mitral and aortic valve disease participating in the ROCKET AF trial. *Eur Heart J*. Dec 14 2014;35:3377–3385.
75. Carnicelli AP, De Caterina R, Halperin JL, et al. Edoxaban for the prevention of thromboembolism in patients with atrial fibrillation and bioprosthetic valves. *Circulation*. Mar 28 2017;135:1273–1275.
76. Guimarães PO, Pokorney SD, Lopes RD, et al. Efficacy and safety of apixaban vs warfarin in patients with atrial fibrillation and prior bioprosthetic valve replacement or valve repair: insights from the ARISTOTLE trial. *Clin Cardiol*. May 2019;42:568–571.

77. Guimarães HP, Lopes RD, de Barros ESPGM, et al. Rivaroxaban in patients with atrial fibrillation and a bioprosthetic mitral valve. *N Engl J Med*. Nov 26 2020;383:2117–2126.
78. Furukawa Y, Miyake M, Fujita T, et al. Rationale, design, and baseline characteristics of the bioprosthetic valves with atrial fibrillation (BPV-AF) study. *Cardiovasc Drugs Ther*. Oct 2020;34:689–696.
79. Karthikeyan G, Connolly SJ, Ntsekhe M, et al. The INVICTUS rheumatic heart disease research program: rationale, design and baseline characteristics of a randomized trial of rivaroxaban compared to vitamin K antagonists in rheumatic valvular disease and atrial fibrillation. *Am Heart J*. Jul 2020;225:69–77.
80. Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med*. Sep 26 2013;369:1206–1214.
81. *FDA Drug Safety Communication: Pradaxa (dabigatran etexilate mesylate) should not be used in patients with mechanical prosthetic heart valves*. Updated 02/13/2018. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-pradaxa-dabigatran-etexilate-mesylate-should-not-be-used-patients. Accessed April 16, 2022.
82. Duraes AR, de Souza Lima Bitar Y, Schonhofen IS, et al. Rivaroxaban versus warfarin in patients with mechanical heart valves: open-label, proof-of-concept trial-the RIWA study. *Am J Cardiovasc Drugs*. May 2021; 21(3):363-371.
83. Jawitz OK, Wang TY, Lopes RD, et al. Rationale and design of PROACT Xa: a randomized, multicenter, open-label, clinical trial to evaluate the efficacy and safety of apixaban versus warfarin in patients with a mechanical On-X Aortic Heart Valve. *Am Heart J*. Sep 2020;227:91–99.
84. Randhawa MS, Vishwanath R, Rai MP, et al. Association between use of warfarin for atrial fibrillation and outcomes among patients with end-stage renal disease: a systematic review and meta-analysis. *JAMA Netw Open*. Apr 1 2020;3:e202175.
85. Stanifer JW, Pokorney SD, Chertow GM, et al. Apixaban versus warfarin in patients with atrial fibrillation and advanced chronic kidney disease. *Circulation*. Apr 28 2020;141:1384–1392.
86. Siontis KC, Zhang X, Eckard A, et al. Outcomes associated with apixaban use in patients with end-stage kidney disease and atrial fibrillation in the United States. *Circulation*. Oct 9 2018;138:1519–1529.
87. Kumbhani DJ, Cannon CP, Beavers CJ, et al. 2020 ACC expert consensus decision pathway for anticoagulant and antiplatelet therapy in patients with atrial fibrillation or venous thromboembolism undergoing percutaneous coronary intervention or with atherosclerotic cardiovascular disease. *J Am Coll Cardiol*. 2021;77:629–658.
88. Yasuda S, Kaikita K, Akao M, et al. Antithrombotic therapy for atrial fibrillation with stable coronary disease. *N Engl J Med*. 2019;381:1103–1113.
89. Chao TF, Liu CJ, Lin YJ, et al. Oral anticoagulation in very elderly patients with atrial fibrillation: a nationwide cohort study. *Circulation*. Jul 3 2018;138:37–47.
90. Kim DH, Pawar A, Gagne JJ, et al. Frailty and clinical outcomes of direct oral anticoagulants versus warfarin in older adults with atrial fibrillation: a cohort study. *Ann Intern Med*. Sep 2021;174:1214–1223.
91. Zhao Y, Yang Y, Tang X, et al. New oral anticoagulants compared to warfarin for perioperative anticoagulation in patients undergoing atrial fibrillation catheter ablation: a meta-analysis of continuous or interrupted new oral anticoagulants during ablation compared to interrupted or continuous warfarin. *J Interv Card Electrophysiol*. Apr 2017;48:267–282.
92. Cardoso R, Knijnik L, Bhonsale A, et al. An updated meta-analysis of novel oral anticoagulants versus vitamin K antagonists for uninterrupted anticoagulation in atrial fibrillation catheter ablation. *Heart Rhythm*. Jan 2018;15:107–115.
93. Cappato R, Marchlinski FE, Hohnloser SH, et al. Uninterrupted rivaroxaban vs. uninterrupted vitamin K antagonists for catheter ablation in non-valvular atrial fibrillation. *Eur Heart J*. Jul 21 2015;36:1805–1811.
94. Calkins H, Willems S, Gerstenfeld EP, et al. Uninterrupted dabigatran versus warfarin for ablation in atrial fibrillation. *N Engl J Med*. Apr 27 2017;376:1627–1636.
95. Kirchhof P, Haeusler KG, Blank B, et al. Apixaban in patients at risk of stroke undergoing atrial fibrillation ablation. *Eur Heart J*. Aug 21 2018;39:2942–2955.
96. Di Biase L, Burkhardt JD, Santangeli P, et al. Periprocedural stroke and bleeding complications in patients undergoing catheter ablation of atrial fibrillation with different anticoagulation management: results from the Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation (AF) Patients Undergoing Catheter Ablation (COMPARE) randomized trial. *Circulation*. Jun 24 2014;129:2638–2644.
97. Nogami A, Harada T, Sekiguchi Y, et al. Safety and efficacy of minimally interrupted dabigatran vs uninterrupted warfarin therapy in adults undergoing atrial fibrillation catheter ablation: a randomized clinical trial. *JAMA Netw Open*. Apr 5 2019;2:e191994.
98. Yu HT, Shim J, Park J, et al. When is it appropriate to stop non-vitamin K antagonist oral anticoagulants before catheter ablation of atrial fibrillation? A multicentre prospective randomized study. *Eur Heart J*. May 14 2019;40:1531–1537.
99. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: executive summary. *Europace*. Jan 1 2018;20:157–208.
100. Yang WY, Du X, Jiang C, et al. The safety of discontinuation of oral anticoagulation therapy after apparently successful atrial fibrillation ablation: a report from the Chinese Atrial Fibrillation Registry study. *Europace*. Jan 1 2020;22:90–99.
101. Proietti R, AlTurki A, Di Biase L, et al. Anticoagulation after catheter ablation of atrial fibrillation: an unnecessary evil? A systematic review and meta-analysis. *J Cardiovasc Electrophysiol*. Apr 2019;30:468–478.
102. Steinberg BA, Peterson ED, Kim S, et al. Use and outcomes associated with bridging during anticoagulation interruptions in patients with atrial fibrillation: findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Circulation*. Feb 3 2015;131:488–494.
103. Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. *N Engl J Med*. Aug 27 2015;373:823–833.
104. Beyer-Westendorf J, Gelbricht V, Förster K, et al. Peri-interventional management of novel oral anticoagulants in daily care: results from the prospective Dresden NOAC registry. *Eur Heart J*. Jul 21 2014;35:1888–1896.
105. Tafur A, Douketis J. Perioperative management of anticoagulant and antiplatelet therapy. *Heart*. Sep 2018;104:1461–1467.
106. Friedman DJ, Piccini JP, Wang T, et al. Association between left atrial appendage occlusion and readmission for thromboembolism among patients with atrial fibrillation undergoing concomitant cardiac surgery. *JAMA*. Jan 23 2018;319:365–374.
107. Yao X, Gersh BJ, Holmes DR, Jr., et al. Association of surgical left atrial appendage occlusion with subsequent stroke and mortality among patients undergoing cardiac surgery. *JAMA*. May 22 2018;319:2116–2126.
108. Holmes DR, Reddy VY, Turi ZG, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet*. Aug 15 2009;374:534–542.
109. Holmes DR, Jr., Kar S, Price MJ, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol*. Jul 8 2014;64:1–12.
110. Lakkireddy D, Thaler D, Ellis CR, et al. Amplatzer amulet left atrial appendage occluder versus watchman device for stroke prophylaxis (Amulet IDE): a randomized, controlled trial. *Circulation*. Nov 9 2021;144:1543–1552.
111. Medical C. WAveCrest Vs. Watchman TranssEptal LAA Closure to REduce AF-Mediated STroke 2 (WAVECREST2). Available at: https://clinicaltrials.gov/ct2/show/NCT03302494. Updated 11.03.2021. Accessed November 20, 2021.