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Non–Vitamin K Antagonist Oral Anticoagulants in the Treatment of Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) increases a patient's stroke risk four- to five-fold. Anticoagulation with the vitamin K antagonist (VKA) warfarin reduces the risk of stroke by 67%, but warfarin carries a significant risk of major bleeding and has unpredictable pharmacodynamics with a narrow therapeutic window, necessitating frequent monitoring of its anticoagulant effect. The non–vitamin K antagonist oral anticoagulants (NOACs) dabigatran, rivaroxaban, apixaban, and edoxaban provide more predictable anticoagulant activity than warfarin with a lower risk of major bleeding, and each is noninferior to warfarin for the prevention of stroke. All have earned regulatory approval in the past eight years. At least one of the NOACs is approved for use in all patients with AF, except those with mechanical valves and rheumatic mitral valve disease, for whom warfarin remains the only option. Recent clinical trials have shown that antithrombotic regimens including NOACs are safe and effective in patients with AF who need potent antiplatelet therapy.

INTRODUCTION

Atrial fibrillation (AF) is a common condition, afflicting 5.1 million Americans and 33.5 million people worldwide (1–3). As the worldwide population ages, the prevalence of AF is expected to increase, with as many as 12 million Americans affected by 2050 and similar increases in other countries (1, 2). AF is characterized by uncoordinated atrial contraction, leading to stasis and subsequent thrombosis of blood within the left atrium and left atrial appendage. When these thrombi are dislodged, they can travel to the brain, causing embolic stroke, or to other systemic arterial beds, causing systemic embolism. Though recent findings have challenged this simplistic mechanistic explanation (4), the clinical data are clear: Without anticoagulation, AF increases the risk of stroke four- to five-fold compared with normal sinus rhythm, and patients with AF have an annual stroke risk of 4.5% (5, 6). In the late 1980s and early 1990s, pivotal randomized controlled trials in patients with AF cumulatively showed that anticoagulation with vitamin K antagonists (VKAs), such as warfarin, reduced the incidence of stroke and systemic embolism by nearly two-thirds compared with placebo and by nearly 40% compared with antiplatelet agents alone. However, VKAs conferred an absolute risk of intracranial hemorrhage as high as 0.3%/year (7, 8).

For this reason, consensus guidelines recommend anticoagulation for stroke prevention in patients with AF at high risk of stroke (9, 10). In these patients, the absolute risk of stroke is high enough that the benefit of anticoagulation outweighs the risk of bleeding. Guidelines further recommend the use of the $CHADS_2$-VASc score to identify patients at high risk (9, 10). When calculating the $CHADS_2$-VASc score, clinicians assign one point each for congestive heart failure, hypertension, age 65–74, diabetes mellitus, vascular disease, and female sex, and two points each for age $\geq$75 and prior stroke or transient ischemic attack (11). Guidelines recommend anticoagulation for patients with $CHADS_2$-VASc $\geq$2 (class I), no anticoagulation for patients with $CHADS_2$-VASc $=$ 0 (class III), and consideration of anticoagulation for patients with $CHADS_2$-VASc $=$ 1 (class IIa) (9, 10).

Warfarin has limitations other than major bleeding. It works by depleting vitamin K stores, preventing the synthesis of coagulation factors II, VII, IX, and X. Warfarin's indirect effect on coagulation means that its effect is mediated by a number of factors, including dietary vitamin K and genetic polymorphisms that affect warfarin's affinity for its target enzyme (12). Moreover, warfarin's metabolism through the cytochrome p450 system leads to interactions with common drugs and foods, which can have unpredictable effects on its anticoagulant effect. These limitations are compounded by warfarin's narrow therapeutic window: Warfarin-treated patients with international normalized ratio (INR) <2 have a relative risk of stroke substantially higher than that of patients with INR $\geq$2, and as INR increases beyond 3, the risk of intracranial hemorrhage increases with no further reduction in stroke risk (10). For these reasons, patients require frequent monitoring of warfarin's anticoagulant effect, as individual patients require different doses of warfarin to achieve adequate anticoagulation, and each patient's dose may fluctuate over time (13). Even with intensive monitoring, the median warfarin-treated patient's INR is within the therapeutic range only 55% of the time (14).

The non–vitamin K antagonist oral anticoagulants (NOACs), which include the direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban, were developed to overcome warfarin's limitations while maintaining its efficacy in stroke prevention. All assert their anticoagulant effect directly, by inhibiting the action of a specific coagulation factor (**Figure 1**), and have a more predictable dose-dependent effect on anticoagulation and a wider therapeutic window compared with warfarin. For this reason, none of the NOACs requires routine monitoring to ensure appropriate anticoagulation. This review focuses on pivotal trials demonstrating the safety and efficacy of NOACs for the prevention of stroke in patients with AF and

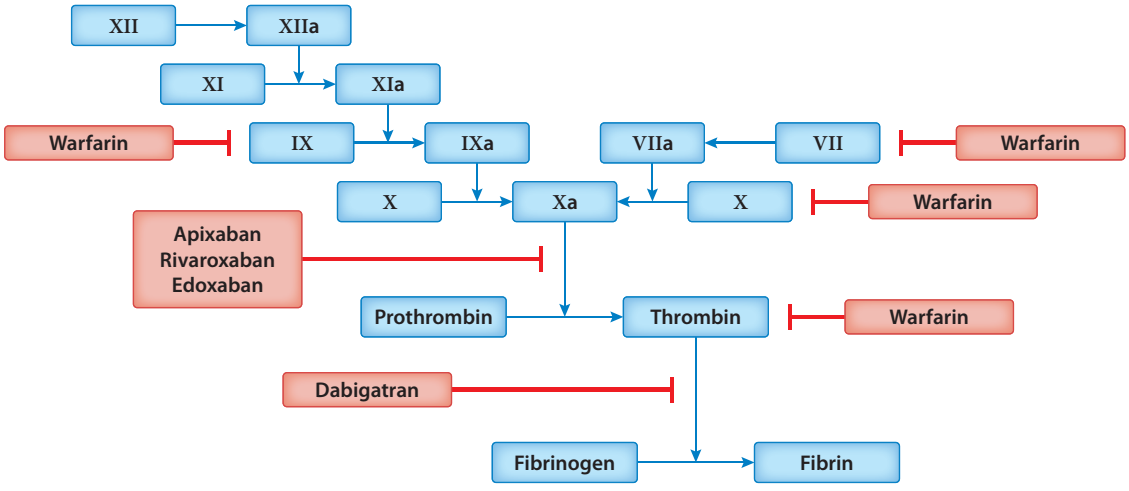

Figure 1

Non–vitamin K antagonist oral anticoagulant (NOAC) mechanisms of action within the coagulation cascade. Dabigatran inhibits factor II; apixaban, rivaroxaban, and edoxaban inhibit factor Xa. Warfarin impairs the synthesis of factors II, VII, IX, and X.

provides guidance for choosing between warfarin and NOACs in selected populations with AF, including patients with mechanical valves, those with valvular heart disease, and those undergoing percutaneous coronary intervention (PCI).

CLINICAL TRIALS COMPARING NON–VITAMIN K ANTAGONIST ORAL ANTICOAGULANTS AND WARFARIN

Noninferiority Studies

Because warfarin's efficacy for stroke prevention in AF had been demonstrated in multiple clinical trials, NOAC clinical trials could not ethically randomize patients to placebo. However, warfarin's limitations were also well recognized, and physicians, patients, and regulatory authorities recognized a clinical need for medications that were as (or nearly as) effective for stroke prevention as warfarin without its risks. For this reason, all NOACs were evaluated head to head versus warfarin in noninferiority studies.

A noninferiority study is designed to test the hypothesis that a new treatment is not worse than an existing treatment by a prespecified amount (15). This prespecified amount is termed the noninferiority margin. If the upper bound of the (usually) one-sided confidence interval (CI) for the hazard ratio (HR) of the new treatment to the old treatment is less than the noninferiority margin, then the new treatment is noninferior to the old treatment. The noninferiority margin can be set at the lower bound of the 95% CI of the treatment effect of the older treatment compared with placebo, so as to ensure that the new treatment is better than placebo, or at a lower value, so as to preserve some portion of the old treatment's benefit over placebo (**Figure 2**). For example, in a meta-analysis of trials comparing warfarin to placebo in patients with AF, the HR for stroke or systemic embolism with placebo compared with warfarin was 2.63, with a 95% CI of 1.92 to 3.57 (7). A putative trial comparing a NOAC to warfarin could use a noninferiority margin of 1.92 to ensure that the NOAC was no worse than placebo; however, all NOAC trials used a noninferiority margin of roughly 1.4, with the intent of preserving 50% of warfarin's stroke reduction benefit compared with placebo.

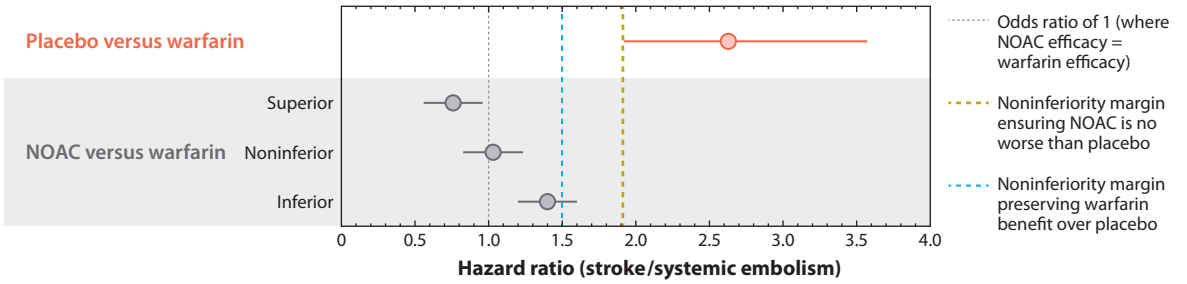

Figure 2

Interpreting noninferiority trials. In noninferiority trials, a treatment is noninferior to another if the upper bound of the 95% confidence interval for that treatment does not cross the prespecified noninferiority boundary. Abbreviation: NOAC, non–vitamin K antagonist oral anticoagulant.

Noninferiority trials must enroll populations that are similar to that included in the trial(s) demonstrating the superiority of the existing treatment over placebo. None of the trials demonstrating warfarin's superiority over placebo for stroke prophylaxis in AF included patients with valvular AF, defined as AF with coexisting rheumatic mitral stenosis, mechanical or bioprosthetic heart valves, or mitral valve repair (9, 10), so the NOAC trials were similarly limited to patients with nonvalvular AF.

Dabigatran

Dabigatran is a direct competitive inhibitor of thrombin that is taken orally twice daily. It has a serum half-life of 12–17 h and is excreted primarily by the kidneys. It was compared with warfarin for the prevention of stroke or systemic embolism in patients with nonvalvular AF in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial (16). RE-LY was a randomized, open-label trial of warfarin (dose-adjusted to maintain an INR of 2.0–3.0) versus dabigatran 150 mg twice daily versus dabigatran 110 mg twice daily. RE-LY enrolled patients with AF plus at least one additional risk factor for stroke: prior stroke or transient ischemic attack, left ventricular ejection fraction (LVEF) <40%, heart failure, age >75, or age 65–74 plus diabetes mellitus, hypertension, or coronary artery disease. Patients with valvular AF or a creatinine clearance <30 mL/min were excluded. There was no protocol for dose reduction in patients with renal insufficiency.

RE-LY enrolled a total of 18,113 patients in 44 countries from December 2005 through December 2007. The median age was 71 years, and the median $CHADS_2$ score was 2.1. (The $CHADS_2$ score is similar to the $CHADS_2$-VASc score but patients receive only one point for age ≥75 and do not receive points for female sex, vascular disease, or age 65–74.) In the warfarin arm, INR was within the therapeutic range 64% of the time. Both the 150 mg and 110 mg doses of dabigatran were noninferior to warfarin for the prevention of stroke or systemic embolism based on a preset noninferiority margin of 1.46, and the 150 mg dose was superior (150 mg: HR 0.66, 95% CI 0.53–0.82; 110 mg: HR 0.91, 95% CI 0.71–1.11) (**Table 1**). The 110 mg dose also reduced the incidence of major bleeding (as defined by the International Society on Thrombosis and Hemostasis) by 20% compared with warfarin; the incidence of major bleeding was similar in the 150 mg dose and warfarin arms.

Importantly, the 110 mg dose of dabigatran was not approved for stroke prevention by the US Food and Drug Administration (FDA), though it was approved in most countries. Instead, in the

Table 1 Major clinical trials of non–vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

Trial	Median age	Mean $CHADS_2$	Mean time in therapeutic range (warfarin)	HR for stroke/ systemic embolism (95% CI)	HR for ISTH major bleeding (95% CI)	HR for all-cause mortality (95% CI)
RE-LY (16)						
Dabigatran 150 mg b.i.d.	71	2.1	64%	0.66 (0.53–0.82)	0.93 (0.81–1.07)	0.88 (0.77–1.00)
Dabigatran 110 mg b.i.d.	71	2.1	64%	0.91 (0.71–1.11)	0.80 (0.69–0.93)	0.91 (0.80–1.03)
ROCKET AF (18)						
Rivaroxaban 20 mg daily	73	3.5	55%	0.79 (0.66–0.96)	1.04 (0.90–1.20)	0.85 (0.70–1.02)
ARISTOTLE (19)						
Apixaban 5 mg b.i.d.	70	2.1	62%	0.79 (0.66–0.95)	0.69 (0.60–0.80)	0.89 (0.80–0.99)
ENGAGE AF (20)						
Edoxaban 60 mg daily	72	2.8	65%	0.79 (0.63–0.99)	0.80 (0.71–0.91)	0.92 (0.83–1.01)
Edoxaban 30 mg daily	72	2.8	65%	1.07 (0.87–1.31)	0.47 (0.41–0.55)	0.87 (0.79–0.96)
Meta-analysis (21)						
NA	NA	NA	NA	0.81 (0.73–0.91)	0.80 (0.65–0.98)	0.90 (0.85–0.95)

Abbreviations: $CHADS_2$, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke (double weight); CI, confidence interval; HR, hazard ratio; ISTH, International Society on Thrombosis and Hemostasis; NA, not applicable.

United States, a 75 mg dose, not tested in RE-LY, was approved for patients with a creatinine clearance of 15–30 mL/min. This dose was based on pharmacodynamic modeling, as no patient had received this dose in any clinical trial.

Rivaroxaban

Rivaroxaban is a direct factor Xa inhibitor that is taken once daily for stroke prophylaxis in AF. It has a serum half-life of 5–9 h and a dual mode of elimination, with roughly one-third eliminated by the kidneys and the remainder metabolized by the liver (17). It was compared with dose-adjusted warfarin in 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), a randomized double-blind trial that enrolled patients with nonvalvular AF and an elevated risk of stroke. Specifically, patients' elevated stroke risk was conferred by either (*a*) a history of stroke, transient ischemic attack, or systemic embolism or (*b*) two of the following stroke risk factors: heart failure or LVEF ≤35%, hypertension, age ≥75 years, or diabetes mellitus (18). Participants randomized to rivaroxaban took a dose of 20 mg once daily, or 15 mg once daily if their creatinine clearance was 30–49 mL/min; patients with creatinine clearance <30 mL/min were excluded.

ROCKET AF enrolled 14,264 patients in 45 countries from December 2006 through June 2009; the median age was 73 and the mean $CHADS_2$ score was 3.5. Based on a noninferiority

margin of 1.46, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism (HR 0.79, 95% CI 0.66–0.96) (**Table 1**). Though this HR and 95% CI suggest rivaroxaban was also superior to warfarin, they are from the less conservative (when evaluating superiority) on-treatment analysis; in the intention-to-treat analysis, rivaroxaban was not superior to warfarin. The incidence of major bleeding was similar in the rivaroxaban and warfarin arms.

Apixaban

Like rivaroxaban, apixaban is a direct factor Xa inhibitor. It is taken twice daily for stroke prophylaxis in AF. It has a half-life of 12 h, and 25% is excreted by the kidneys. Apixaban was compared with dose-adjusted warfarin in the randomized double-blind ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial (19). ARISTOTLE enrolled patients with nonvalvular AF plus at least one risk factor for stroke or systemic embolism: age ≥75 years; prior stroke, transient ischemic attack, or systemic embolism; heart failure or LVEF ≤40%; diabetes mellitus; or hypertension. Patients with creatinine clearance <25 mL/min or serum creatinine >2.5 mg/dL were excluded. Patients randomized to apixaban were treated with 5 mg twice daily; 2.5 mg doses were used in patients with at least two of the following criteria: age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL.

ARISTOTLE enrolled 18,201 patients in 39 countries from December 2006 through April 2010. Apixaban was noninferior (based on a noninferiority margin of 1.44) and superior to warfarin for the prevention of stroke or systemic embolism (HR 0.79, 95% CI 0.66–0.95), and it also reduced the incidence of major bleeding compared with warfarin (HR 0.69, 95% CI 0.60–0.80) (**Table 1**). Unique among the NOAC trials, ARISTOTLE demonstrated that apixaban reduced all-cause mortality compared with warfarin.

Edoxaban

Like rivaroxaban and apixaban, edoxaban is an oral direct factor Xa inhibitor. Like rivaroxaban, it is taken once daily for stroke prophylaxis in AF. It has a half-life of 10–14 h, and 50% is cleared by the kidneys. Its efficacy for stroke prophylaxis compared with dose-adjusted warfarin was evaluated in the randomized double-blind ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48) trial (20). ENGAGE AF enrolled patients with nonvalvular AF and a $CHADS_2$ score ≥2; patients with creatinine clearance <30 mL/min were excluded. Participants were randomized to dose-adjusted warfarin, 60 mg edoxaban daily, or 30 mg edoxaban daily. For participants randomized to either edoxaban dose, the dose was halved for those with a creatinine clearance 30–50 mL/min, body weight ≤60 kg, or the concomitant use of verapamil or quinidine.

ENGAGE AF enrolled 21,105 patients in 46 countries from November 2008 through November 2010. Both doses of edoxaban were noninferior to warfarin for the prevention of stroke or systemic embolism (based on a noninferiority margin of 1.38), and the 60 mg dose was superior (60 mg: HR 0.79, 95% CI 0.63–0.99; 30 mg: HR 1.07, 95% CI 0.87–1.31) (**Table 1**). Both doses caused less major bleeding than warfarin did, with the 30 mg dose reducing major bleeding by 53%.

The FDA ultimately approved only the 60 mg dose, with instructions to reduce the dose to 30 mg daily in patients with creatinine clearance 15–50 mL/min. In ENGAGE AF, patients with creatinine clearance >95 mL/min (<5% of patients enrolled in the trial) had a higher incidence of stroke when treated with edoxaban compared with warfarin, and edoxaban is contraindicated in patients with a creatinine clearance >95 mL/min (20).

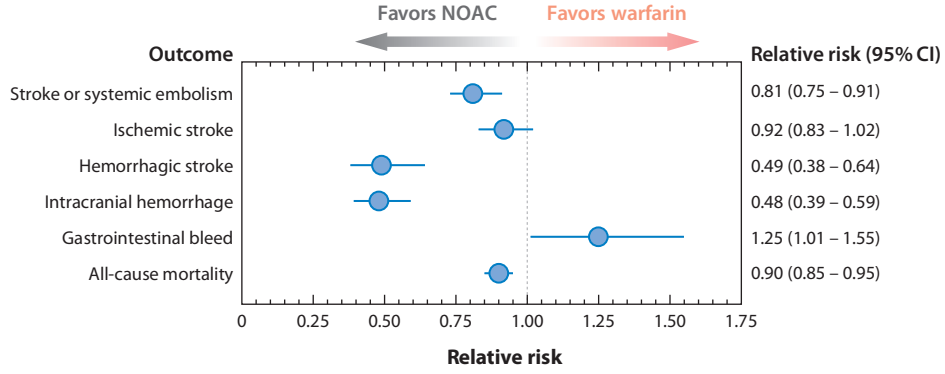

Figure 3

Effectiveness and safety of non–vitamin K antagonist oral anticoagulants (NOACs), as a class, compared with warfarin (21). When data from pivotal clinical trials are pooled (by meta-analysis), treatment with a NOAC is associated with a lower risk of stroke and systemic embolism, driven by a lower risk of hemorrhagic stroke, and a lower risk of mortality compared with warfarin.

Meta-Analysis of NOACs Versus Warfarin

In a meta-analysis that pooled the results of the pivotal clinical trials comparing the NOACs and warfarin, patients randomized to NOACs had a 19% lower risk of stroke or systemic embolism, driven by a 51% lower risk of hemorrhagic stroke (**Figure 3**) (21). There was no significant difference in the rate of ischemic stroke, and NOACs increased the risk of gastrointestinal bleeding by 25% compared with warfarin. Compared with warfarin, patients randomized to NOACs had a statistically significant 10% lower relative risk of all-cause death.

Efficacy and Safety Data in Observational Analyses

Like most clinical trials, RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF enrolled a carefully selected patient population. For this reason, many patients who might receive NOACs in clinical practice were not represented in these trials. Of patients with AF and $CHADS_2$-VASc $\geq$1 in the United Kingdom, between 51% and 68% met all inclusion and no exclusion criteria for each of the pivotal NOAC trials (22). Among patients on hemodialysis for end-stage renal disease, 12% of patients requiring anticoagulation were started on NOACs (23). Investigators have employed multiple observational study designs to evaluate outcomes of NOACs when taken in routine clinical practice.

The Xarelto for Prevention of Stroke in Patients with Atrial Fibrillation (XANTUS) study was a prospective nonrandomized single-arm postmarketing clinical trial of patients with AF prescribed rivaroxaban (24, 25). To reduce selection bias, all patients $\geq$18 years old prescribed rivaroxaban for AF at participating sites were screened and approached for study enrollment. In XANTUS, the stroke or systemic embolism rate was 0.8 per 100 patient-years, and the major bleeding rate was 2.1 per 100 patient-years—both lower than in the rivaroxaban arm of ROCKET AF, consistent with the fact that ROCKET AF's inclusion criteria enriched for patients at higher risk of stroke (25). XANTUS had no warfarin or other control arm, so it does not answer questions about the comparative effectiveness and safety of NOACs and warfarin in routine clinical practice.

Some retrospective cohort studies have attempted to answer these questions. The results of these studies have been somewhat heterogeneous, especially with respect to the endpoint of stroke or systemic embolism. In general, they show that NOACs are less effective than warfarin at

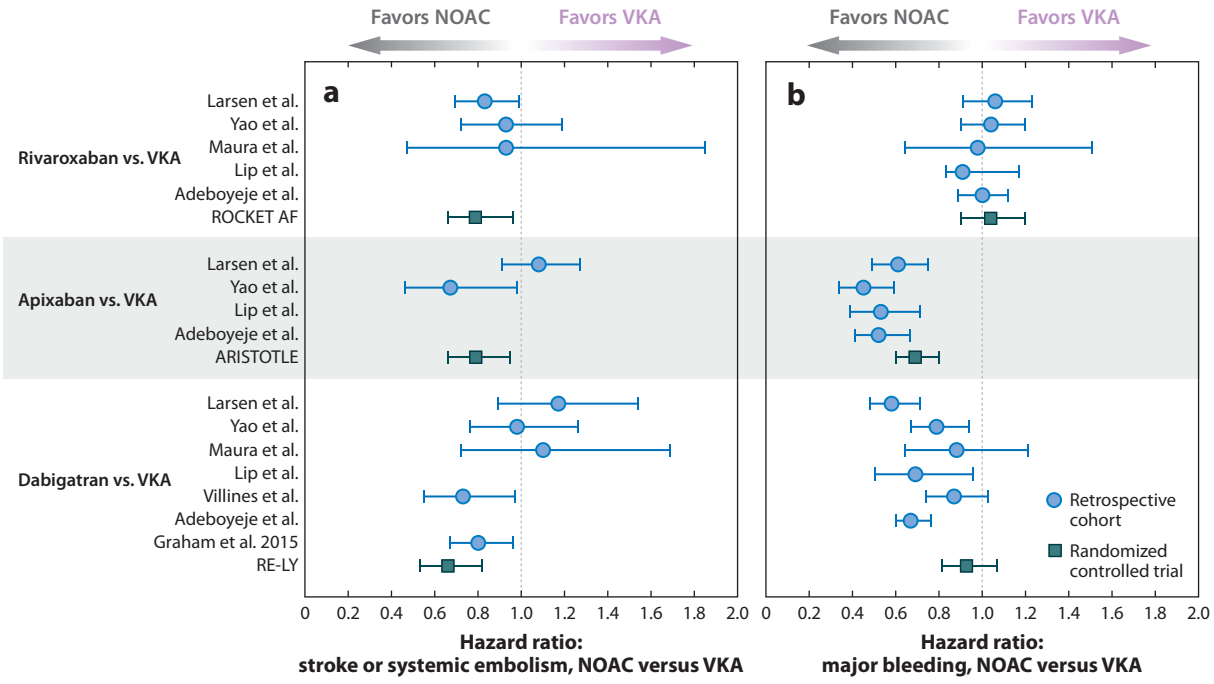

Figure 4

Comparative effectiveness (*a*) and safety (*b*) of non–vitamin K antagonist oral anticoagulants (NOACs) compared with warfarin (vitamin K antagonist, VKA) in selected observational studies and pivotal clinical trials. Observational studies, in general, have overestimated the effectiveness of NOACs and underestimated their safety compared with pivotal randomized clinical trials.

preventing stroke or systemic embolism than they appeared in the pivotal clinical trials but are more effective at preventing major bleeding (**Figure 4**) (26–33).

In addition to the different patient populations included in the observational analyses compared with the clinical trials, one potential reason for the discrepancy in results is inappropriate NOAC dosing. All NOACs have criteria for dose reduction based on renal function, weight, and/or age, and studies using pharmacy claims data have shown a higher proportion of patients receiving dose-reduced NOACs than would be expected based on rates of chronic kidney disease (32). In a multicenter United States–based registry, 10% of NOAC patients were underdosed and 3% were overdosed (34). Compared with properly dosed patients, underdosed patients were more likely to have stroke or systemic embolism, more likely to be hospitalized for cardiovascular causes, and more likely to die (34).

Aspirin for Stroke Prophylaxis in Atrial Fibrillation

Aspirin is prescribed for stroke prophylaxis in greater than one-third of patients with AF and $CHADS_2$-VASc ≥ 2 (35), despite guidelines recommending treatment with oral anticoagulation in these patients. Compared with placebo, aspirin reduces the risk of stroke by 27%, but increases risk by 39% compared with warfarin (7). Clinicians may choose aspirin over oral anticoagulation in these patients in an attempt to minimize bleeding risk; however, compared with aspirin, warfarin (dose adjusted to target an INR of 2.0–3.5) did not significantly increase the risk of major bleeding in a meta-analysis of clinical trials (36). Aspirin was also compared with apixaban in patients with

AF for whom warfarin was unsuitable in the randomized double-blind AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) study (37). Inclusion and exclusion criteria for AVERROES were similar to ARISTOTLE's, but patients had to be judged ineligible to receive warfarin by their treating physician. AVERROES was stopped early due to overwhelming benefit in the apixaban arm. Compared with aspirin, apixaban reduced the incidence of stroke or systemic embolism by 55% (HR 0.45, 95% CI 0.32–0.62) with similar rates of major bleeding (HR 1.13, 95% CI 0.74–1.75).

In patients with stable coronary artery disease and AF, guidelines generally recommend use of an oral anticoagulant alone, without aspirin (9, 10). These recommendations are not supported by randomized clinical trial evidence, but by observational studies. In a cohort of 2,743 Danish patients with AF and stable coronary artery disease treated with a VKA, 65% were treated with an antiplatelet agent in addition to the VKA (38). Compared with VKA monotherapy, treatment with a VKA plus an antiplatelet agent was associated with a similar incidence of cardiovascular death and myocardial infarction, but a significantly higher rate of major bleeding.

In patients with AF with recent myocardial infarction (MI) or PCI and an indication for dual antiplatelet therapy (aspirin plus clopidogrel) in addition to an oral anticoagulant, guidelines recommend adding a VKA to either dual antiplatelet therapy or clopidogrel (9, 10). However, recent clinical trials have evaluated NOACs in combination with dual or single antiplatelet therapy in this population (see the section titled Non–Vitamin K Antagonist Oral Anticoagulants in the Patient Undergoing Percutaneous Coronary Intervention, below).

CHOOSING AN ANTICOAGULATION STRATEGY

Though the NOACs are generally both safer and more efficacious than warfarin, they do have several disadvantages compared with warfarin that may lead physicians to use warfarin in certain patients.

First, the NOACs have not been extensively tested in patients with severe renal dysfunction (creatinine clearance <15–30 mL/min) or end-stage renal disease, and only apixaban is approved in this cohort of patients. Ongoing clinical trials in this patient population will clarify the role of NOACs (NCT02942407, NCT02933697).

Second, NOACs are contraindicated in patients with valvular AF, including patients with rheumatic mitral stenosis and mechanical heart valves. These patients were excluded from the pivotal clinical trials demonstrating NOACs' efficacy and safety. Subsequently, RE-ALIGN (the Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement) compared the safety and efficacy of dabigatran versus warfarin in patients with mechanical heart valves. In RE-ALIGN, patients randomized to dabigatran had higher rates of both stroke and major bleeding compared with the warfarin arm (39). Importantly, however, pivotal clinical trials of NOACs versus warfarin did not exclude patients with valvular heart disease other than rheumatic mitral stenosis or mechanical heart valves, and it may be safe to treat these patients with NOACs. All four pivotal NOAC clinical trials have published analyses of the subgroup of patients with valvular heart disease (40–43). In each case, the benefits of NOACs compared with warfarin for the prevention of stroke or systemic embolism and the reduction in major bleeding were consistent in patients with and without valvular heart disease (44).

The third reason that physicians may choose warfarin over NOACs is affordability. One study showed that for the first six months of therapy, patients with health insurance who were started on warfarin spent $54 out of pocket, whereas those initiating dabigatran and rivaroxaban spent

$205 and $221, respectively (45). For uninsured patients, these differences may be even more pronounced: 30-day supplies of dabigatran, rivaroxaban, apixaban, and edoxaban cost $387, $405, $430, and $350, respectively, compared with $4 for warfarin (**https://www.goodrx.com**).

Lastly, physicians may choose to use warfarin in patients who have had prior difficulties with medication adherence. Because warfarin prevents synthesis of coagulation factors, its anticoagulant effect lasts several days, and a patient missing a single dose remains protected against embolic events. By contrast, the NOACs are competitive inhibitors of coagulation factors, and their effect lasts only as long as they are present in the body. All have half-lives of 5–12 h, meaning that a patient missing a dose may not be protected against embolic events. The twice-daily dosing schedules of dabigatran and apixaban (compared with once-daily warfarin) also make adherence more difficult.

When the NOACs were first made available, some physicians and patients were hesitant to use them because a reversal agent was not available, in contrast to warfarin, which can be reversed with vitamin K. Though the NOACs impair coagulation for relatively short durations after stopping compared with warfarin, their half-lives may be longer in patients with impaired renal function (46). Dabigatran now has an FDA-approved reversal agent, and clinical trials of a reversal agent for apixaban, rivaroxaban, and edoxaban are ongoing (47, 48).

Immediately upon availability, NOACs also had not been evaluated in patients with a need for concurrent antiplatelet therapy. However, clinical trials comparing NOACs and warfarin in patients with AF with recent MI or PCI have been recently completed or are ongoing (see the section titled Non–Vitamin K Antagonist Oral Anticoagulants in the Patient Undergoing Percutaneous Coronary Intervention, below).

Choosing Between NOACs

The NOACs have not been evaluated in head-to-head clinical trials, but they have been compared using other study designs. Several network meta-analyses and observational analyses have been published, and the results are inconsistent. Network meta-analysis is a statistical technique that enables indirect comparison between two treatment strategies that have been tested against a common comparator but not directly against each other. One network meta-analysis ranked dabigatran as the best agent for prevention of stroke or systemic embolism and apixaban as the best agent for major bleeding (49); other network meta-analyses found that rivaroxaban was most efficacious for prevention of stroke or systemic embolism and that edoxaban had the lowest incidence of major bleeding (50, 51). These network meta-analyses are limited by heterogeneity in study design between the major NOAC clinical trials (52).

Retrospective analyses have similarly been inconsistent. In a retrospective analysis of a US administrative claims database, Noseworthy et al. (53) found no difference in the rate of stroke or systemic embolism in patients treated with apixaban, rivaroxaban, and dabigatran but found that apixaban was associated with a lower rate of major bleeding compared with rivaroxaban and dabigatran. In another retrospective analysis, Graham et al. (54) found that rivaroxaban was associated with a lower rate of stroke or systemic embolism compared with dabigatran. All analyses using observational data are also limited by unmeasured confounding. In the absence of randomized clinical trials comparing NOACs head to head, their comparative effectiveness and safety remain unknown, and one cannot be recommended over another.

Instead, when choosing between NOACs, physicians should generally take patients' renal function and concomitant medications into consideration (**Table 2**). All NOACs except apixaban are contraindicated in patients with a creatinine clearance <15 mL/min, and edoxaban is contraindicated in patients with a creatinine clearance >95 mL/min. The NOACs are metabolized

Table 2 Selecting the best anticoagulant for each patient

Patient characteristic	Warfarin	Apixaban	Dabigatran	Rivaroxaban	Edoxaban
Desires effective prevention of stroke or systemic embolism	✓	✓	✓	✓	✓
Desires lower risk of major bleeding than warfarin	✗	✓	✓	✓	✓
Severe renal dysfunction (CrCl <15 mL/min) or end-stage renal disease	✓	✓	✗	✗	✗
Excellent renal function (CrCl >95 mL/min)	✓	✓	✓	✓	✗
Concerned about need for reversal agent	✓	✗	✓	✗	✗
Recent MI or PCI with need for $P2Y_{12}$ inhibitor therapy	*	*	✓	✓	*
Difficulty with adherence	✓	✗	✗	*	*
Mechanical valve or rheumatic mitral valve disease	✓	✗	✗	✗	✗
Other valvular heart disease	✓	✓	✓	✓	✓
Financial hardship	✓	✗	✗	✗	✗
Desires to avoid clinic visits for monitoring	✗	✓	✓	✓	✓
Desires to avoid dietary limitations	✗	✓	✓	✓	✓

Abbreviations: CrCl, creatinine clearance; MI, myocardial infarction; PCI, percutaneous coronary intervention. Symbols: red X, avoid; green checkmark, okay to use; yellow asterisk, proceed with caution.

by different pathways, and each interacts with a different set of medications (55). If a patient is taking a medication that strongly interacts with one of the NOACs, a different NOAC can often be chosen.

NON–VITAMIN K ANTAGONIST ORAL ANTICOAGULANTS IN THE PATIENT UNDERGOING PERCUTANEOUS CORONARY INTERVENTION

Though patients with an indication for dual antiplatelet therapy with aspirin and clopidogrel (such as those with MI or undergoing PCI) were excluded from the pivotal clinical trials leading to NOAC approval, up to 40% of patients with incident AF will be diagnosed with MI over long-term follow-up (56). Patients with AF and MI treated with triple antithrombotic therapy (warfarin, aspirin, and a $P2Y_{12}$ inhibitor) have very high rates of bleeding, with 12% hospitalized for bleeding in the first year after starting triple therapy and 2% suffering an intracranial hemorrhage (57). The suboptimal outcomes on traditional triple therapy have motivated clinical trials comparing traditional triple therapy to combinations of agents that include a NOAC in patients with AF undergoing PCI.

PIONEER AF-PCI (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention) compared three antithrombotic strategies: (*a*) warfarin, aspirin, and a $P2Y_{12}$ inhibitor; (*b*) low-dose rivaroxaban (15 mg once daily) and a $P2Y_{12}$ inhibitor; and (*c*) very-low-dose rivaroxaban (2.5 mg once daily), aspirin, and a $P2Y_{12}$ inhibitor (58). Compared with traditional therapy with warfarin, aspirin, and clopidogrel, both rivaroxaban-containing regimens reduced the incidence of major bleeding, by 41% in the low-dose rivaroxaban arm and 37% in the very-low-dose rivaroxaban arm. The incidence of the composite of cardiovascular death, MI, or stroke was similar in the three groups, though the trial was underpowered to detect a difference in this outcome.

RE-DUAL PCI (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) compared three antithrombotic strategies in patients with AF undergoing PCI: (*a*) traditional therapy with warfarin, aspirin, and a $P2Y_{12}$ inhibitor; (*b*) 150 mg dabigatran twice daily and a $P2Y_{12}$ inhibitor without aspirin; and (*c*) 110 mg dabigatran twice daily and a $P2Y_{12}$ inhibitor without aspirin. Patients randomized to dabigatran 110 mg twice daily had a 48% lower incidence of major bleeding than patients randomized to the warfarin-containing regimen, and patients randomized to the 150 mg dose had a 27% lower incidence of major bleeding than patients randomized to warfarin. The dabigatran-containing regimens were noninferior to warfarin-containing regimens for the prevention of a composite of ischemic events including death, stroke, systemic embolism, myocardial infarction, and unplanned revascularization.

Taken together, these two trials demonstrate that regimens comprising a NOAC and a $P2Y_{12}$ inhibitor reduce the incidence of major bleeding compared with warfarin-containing regimens used as triple antithrombotic therapy (aspirin + clopidogrel + warfarin), and may be similarly effective for the prevention of stroke and systemic embolism. Ongoing clinical trials testing apixaban and edoxaban in this patient population will further clarify this issue (NCT02415400, NCT02866175).

CONCLUSIONS

The NOACs, including the direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban, have been approved by regulatory authorities for the prevention of stroke in patients with AF in the past eight years. Each NOAC is at least as efficacious as warfarin for the prevention of stroke or systemic embolism in patients with nonvalvular AF, and each causes fewer severe bleeding episodes. As a class, NOACs lower mortality and reduce the incidence of intracranial bleeding compared with warfarin. Despite these findings, physicians should use warfarin rather than a NOAC in patients with valvular AF (rheumatic mitral stenosis or mechanical heart valve) and may choose to use warfarin rather than a NOAC in patients with severe renal dysfunction, financial hardship, or difficulties with adherence. Though patients with a requirement for dual antiplatelet therapy were not included in pivotal NOAC clinical trials, recent data suggest that antithrombotic regimens including NOACs are at least as safe as traditional triple antithrombotic therapy with warfarin and dual antiplatelet therapy in patients with MI or patients undergoing PCI. The NOACs have not been compared to each other in head-to-head trials, and decisions regarding which NOAC to choose should be based on renal function, medication interactions, and dosing frequency.

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