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Transition of Patients From Blinded Study Drug to Open-Label Anticoagulation

The ENGAGE AF–TIMI 48 Trial

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ABSTRACT

BACKGROUND At the end of 2 previous trials, an excess of stroke and bleeding was observed in patients with AF randomized to a new oral anticoagulant (NOAC) who transitioned to a vitamin K antagonist (VKA).

OBJECTIVES The ENGAGE AF–TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation—Thrombolysis in Myocardial Infarction 48) trial compared once-daily edoxaban to warfarin for stroke prevention in patients with AF. An end-of-trial transition plan was developed to minimize the risks of stroke due to inadequate anticoagulation and bleeding from excessive anticoagulation during this critical period.

METHODS All patients on the blinded study drug at the trial's conclusion were included in this analysis. In pre-specified analyses, stroke, bleeding, and death that occurred through 30 days after the end-of-trial visit were stratified by randomized treatment allocation and open-label anticoagulant selected post-trial.

RESULTS Of the 13,642 patients taking the blinded study drug at the end of the trial, 9,304 (68.2%) were transitioned to open-label VKA and 4,258 patients (31.2%) to an NOAC. There were 21 strokes evenly distributed across the 3 randomized treatment arms: warfarin 7 (1.90%/year), edoxaban high dose 7 (1.89%/year), edoxaban low dose 7 (1.85%/year). Major bleeding was also similar across the 3 treatment arms: warfarin 11 (2.98%/year), edoxaban high dose 10 (2.69%/year), edoxaban low dose 18 (4.76%/year). In patients transitioned to VKA, 85% of patients had at least 1 INR ≥2 by day 14 after the transition and 99% by day 30.

CONCLUSIONS The ENGAGE AF–TIMI 48 transition plan protected patients from an excess of thrombotic and bleeding events and should be helpful in clinical practice when patients are transitioned between oral anticoagulants. (Global Study to Assess the Safety and Effectiveness of Edoxaban [DU-176b] vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation [EngageAFTIMI48]; NCT00781391) (J Am Coll Cardiol 2014;64:576–84)
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Atrial fibrillation (AF) predisposes patients to an increased risk of embolic stroke and is associated with a higher mortality rate than sinus rhythm (1–3). Warfarin and other vitamin K antagonists (VKAs) are highly effective in preventing stroke, but limited by their narrow therapeutic window and inconveniences imposed by the need for coagulation monitoring and frequent dose adjustments (4–6).

Four new oral anticoagulants (NOACs) that inhibit thrombin or activated factor X (factor Xa) in a dose-dependent fashion and do not require regular monitoring have been found to be at least as effective and safe as warfarin for preventing stroke and systemic embolic events (SEE) in patients with AF in their respective phase 3 trials (7–10). In the 2 previous trials

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investigating factor Xa inhibitors, 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) (11) and ARISTOTLE (Apixaban for Reduction In STroke and Other Thromboembolic Events in Atrial Fibrillation) (12) trials, there was an excess of both thrombotic and bleeding events in the 30 days after the end of the trial when patients were transitioned from the blinded study drug to open-label antithrombotic therapy.

In the ROCKET AF trial, there was a more than 3-fold increase in stroke or SEE (blinded rivaroxaban to open-label VKA: 22 events [6.42%/year] vs. blinded warfarin to open-label VKA: 6 events [1.73%/year]) and major bleeding (blinded rivaroxaban to open-label VKA: 25 events [7.29%/year] vs. blinded warfarin to open-label VKA: 7 events [2.01%/year]) in patients randomized to rivaroxaban compared with warfarin who transitioned to open-label VKA at the end of the trial (11). In the ARISTOTLE trial, a 2-day bridging period with apixaban (in patients randomized to apixaban) or placebo (in patients randomized to warfarin) in addition to open-label VKA was employed to mitigate the increased risk of stroke. However, an excess of thrombotic (stroke or SEE: blinded apixaban to open-label VKA: 21 events [4.02%/year] vs. blinded warfarin to open-label VKA: 5 events [0.99%/year]) and major bleeding (blinded apixaban to open-label VKA: 26 events [4.97%/year] vs. blinded warfarin to open-label VKA: 10 events [1.97%/year]) were seen in the 30-day period after the trial in patients randomized to apixaban compared with warfarin (12). Events after the end of the open-label RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial were not reported, and selected patients still on dabigatran at the completion of the trial were eligible to continue dabigatran as part of a long-term, open-label extension study (RELY-ABLE [Long-term Multicenter Extension of Dabigatran Treatment in Patients with Atrial Fibrillation]) (7,13). The U.S. Food and Drug Administration has issued a "boxed warning" in the prescribing information for dabigatran, rivaroxaban, and apixaban, cautioning providers that discontinuation of therapy could increase the risk of thrombotic events (14–16).

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

factor Xa = activated factor X

INR = international normalized ratio

NOAC = new oral anticoagulant

SEE = systemic embolic event

TIMI = thrombolysis in myocardial infarction

VKA = vitamin K antagonist

The ENGAGE-AF-TIMI 48 trial (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48) was a randomized, double-blind, double-dummy trial comparing 2 once-daily edoxaban dose-regimens of warfarin in 21,105 patients with AF at moderate to high risk of stroke (10,17). Prior to trial completion, a transition plan was developed to protect patients transitioning to open-label VKA or an NOAC at the trial's end by minimizing both the risk of ischemic stroke due to inadequate anticoagulation and the risk of bleeding with excessive anticoagulation while maintaining the integrity of the blinding to the treatment allocation. This was the first trial with a robust experience of patients transitioning to an open-label NOAC (n = 4,258) and provides information on the efficacy and safety of transitions between all available anticoagulants: VKA to all 3 approved NOACs (dabigatran, rivaroxaban, apixaban) and edoxaban to VKA or 1 of the 3 other NOACs.

We hypothesized that a comprehensive transition plan described below would protect patients transitioning from blinded to open-label anticoagulation at the end of the trial by minimizing both the risk of ischemic stroke due to inadequate anticoagulation and the risk of bleeding with excessive anticoagulation. Evidence-based guidance is needed in this area as patients in clinical practice are frequently switched from 1 anticoagulant to another before and after procedures when they develop side effects from a particular anticoagulant or need to switch due to changes in insurance coverage or are prescribed a necessary, but contraindicated, medication.

METHODS

STUDY POPULATION. The ENGAGE AF-TIMI 48 trial has been described previously (17). Eligible patients were ≥21 years of age with AF documented on an electrical tracing within 12 months, a $CHADS_2$ risk score ≥2, and anticoagulation planned for the trial

duration. Patients were randomly assigned (1:1:1) to receive warfarin, dose-adjusted to an international normalized ratio (INR) of 2.0 to 3.0, high-dose edoxaban (60 mg once daily) or low-dose edoxaban (30 mg once daily). The dose of edoxaban was reduced by half, if any of the following were present at randomization or during the course of the trial: creatinine clearance 30 to 50 ml/min; body weight ≤ 60 kg; or concomitant verapamil, quinidine, or dronaderone (potent P-glycoprotein inhibitors). To be eligible for the transition plan and to be included in this analysis, patients had to have been on a blinded study drug within 3 days of their end-of-trial visit. Patients off the study drug for >3 days were encouraged to resume anticoagulation as clinically indicated but were not included in this analysis, as they were not therapeutically anticoagulated at their end-of-trial visit and did not require a transition from the blinded study drug to open-label anticoagulation.

TABLE 1 Baseline Characteristics

Characteristic	All Patients Randomized (N = 21,105)	Patients on Study Drug at End of Trial		
		Warfarin (n = 4,503)	Edoxaban High Dose (n = 4,526)	Edoxaban Low Dose (n = 4,613)
Age, yrs	72 (64–78)	70 (63–76)	71 (63–76)	71 (63–77)
Age ≥75 yrs, %	40.2	34.0	34.3	35.6
Female, %	38.1	36.8	36.0	37.9
Region, %				
North America	22.2	20.0	19.5	19.3
Latin America	12.6	11.9	12.4	12.4
Western Europe	15.3	14.5	14.4	14.5
Eastern Europe	33.8	37.5	37.3	37.2
Asia-Pacific and South Africa	16.0	16.1	16.3	16.6
AF type, %				
Paroxysmal	25.4	25.0	24.6	25.7
Persistent	23.1	22.8	22.8	22.6
Permanent	51.5	52.3	52.6	51.7
$CHADS_2$ score (mean)	2.8	2.8	2.8	2.8
≤3, %	77.4	79.5	79.3	79.4
4–6, %	22.6	20.5	20.7	20.6
Previous stroke or TIA, %	28.3	28.0	27.9	28.2
Heart failure, %	57.4	57.1	58.2	56.0
Diabetes, %	36.1	35.8	35.8	36.6
Hypertension, %	93.6	94.1	93.7	94.1
Prior myocardial infarction, %	11.5	10.3	10.1	10.7
VKA experienced, %	58.9	60.8	59.3	60
Dose reduction at randomization*, %	25.4	20.4	20.7	21.1
Medications at time of randomization, %				
Aspirin	29.3	27.6	28.3	28.1
Thienopyridine	2.3	1.8	2.1	1.9
Amiodarone	11.8	11.7	12.0	11.4
Digoxin or digitalis preparation	30.0	29.8	28.9	28.5

Values are median (interquartile range) or n (%). *Patients with a creatinine clearance ≤50 ml/min or body weight 60 kg or less, as well as patients who were receiving the concomitant strong P-glycoprotein inhibitors verapamil or quinidine at randomization, received a 50% reduction in the dose of edoxaban to maintain similar exposure to the patients who did not have any of these 3 factors. Some patients had more than 1 reason for dose adjustment.

AF = atrial fibrillation; $CHADS_2$ = stroke risk factor scoring system where 1 point is given for history of congestive heart failure (C), hypertension (H), age ≥75 years (A), diabetes (D), and 2 points given for history of stroke or transient ischemic attack (S); TIA = transient ischemic attack; VKA = vitamin K antagonist.

END-OF-TRIAL TRANSITION PLAN. The end-of-trial transition plan consisted of 4 key components: 1) selection of the oral anticoagulant (VKA or an NOAC) by the treating physician and patient; 2) a 14-day transition kit of modified-dose edoxaban for patients randomized to edoxaban (30 mg once daily for patients in whom the edoxaban dose was not reduced before the end-of-trial visit and 15 mg once daily for patients in whom the edoxaban dose had been reduced before the end-of-trial visit, regardless of randomized edoxaban drug assignment) or matching placebo for patients randomized to warfarin (Online Table 1); 3) early and frequent INR testing (≥3 tests during the first 2 weeks); and 4) use of a VKA titration algorithm.

At the end-of-trial visit, INR was measured with a point-of-care device and a prescription for the intended open-label anticoagulant (VKA or NOAC) was provided. The transition kit was provided only to patients who were transitioning to open-label VKA and was continued until an open-label INR ≥2 was achieved or until day 14 (whichever occurred first). If the INR was <2.0 during the transition period, the patient continued on the transition kit (up to 14 days) with aggressive titration of open-label VKA dose as recommended by the protocol algorithm (Online Table 2). INR measurements were mandated at days 4 to 6, 7 to 10, and 11 to 14 and as often as needed through day 30 until the patient was confirmed to be in therapeutic range. Open-label INR testing was not allowed on days 1 to 3 to avoid unblinding so as to maintain the integrity of the trial.

Patients transitioning to an NOAC were not given a transition kit (active edoxaban or matching placebo). If the INR was <2.0 at the end-of-trial visit, the patient was started on an open-label NOAC the following day and if the INR was ≥2.0 the patient returned for an open-label INR measurement on days 4 to 6 (and every 1 to 4 days thereafter, if necessary), until the INR was <2.0, at which time the open-label NOAC was begun on the same day. All patients were followed for a minimum of 30 days after their end-of-trial visit.

STATISTICAL ANALYSIS. Evaluation of the efficacy and safety at the end-of-study transition plan in the ENGAGE AF-TIMI 48 trial was pre-specified. Descriptive statistics of baseline characteristics were

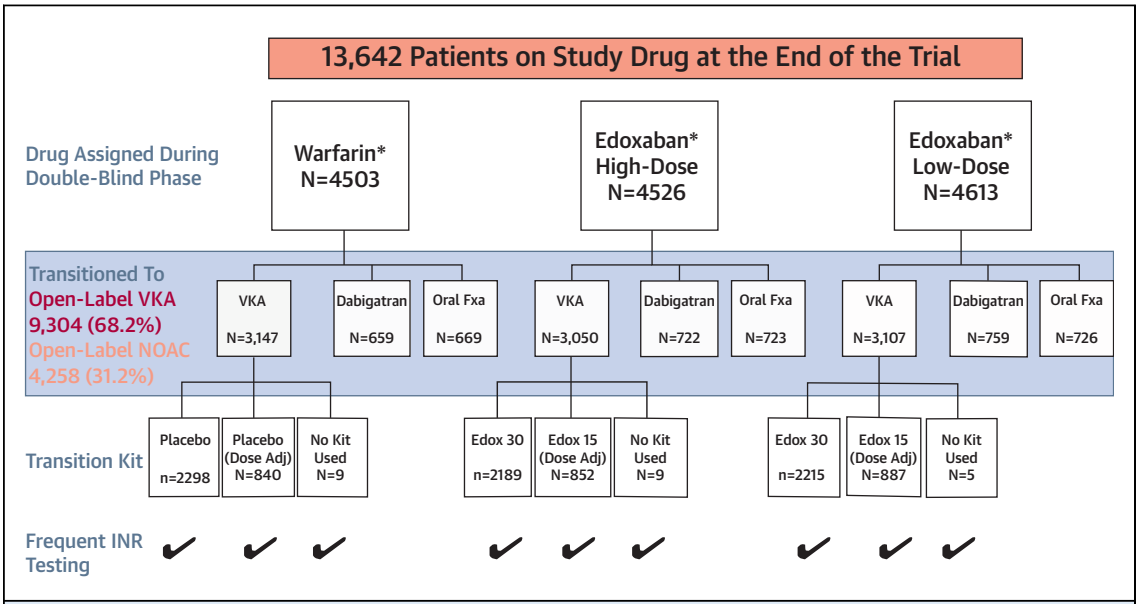


FIGURE 1 End-of-Trial Transition to Open-Label Anticoagulation

*There were 12, 11, and 10 patients who transitioned to antiplatelet therapy alone in the warfarin, edoxaban high-dose, and edoxaban low-dose groups, respectively. There were 16, 20, and 11 patients who transitioned to no antithrombotic therapy in the warfarin, edoxaban high-dose, and edoxaban low-dose groups, respectively. Frequent international normalized ratio (INR) testing = at least 3 INR tests performed in days 4 to 14 during the transition phase with continued INR testing days 15 to 30 if vitamin K antagonist (VKA) dose changes or if INR was not in the therapeutic range (2.0 to 3.0). FXa = activated factor X.

given as numbers and percentages, medians with 25th and 75th percentiles, or means with standard deviations. Events that occurred between the end-of-trial visit of double-blind therapy and 30 days later were included in this analysis. Event rates were expressed per 100 patient-years. To determine if there was an increase in bleeding during the period when the transition kit and open-label VKA were given together, rates of major bleeding in the 3 treatment arms were compared from days 1 to 14 in addition to days 1 to 30. The independent clinical endpoint committee, which was unaware of randomized treatment assignment, adjudicated all events.

Outcomes included all-cause stroke or SEE, ischemic stroke, hemorrhagic stroke, all-cause mortality, major bleeding (defined by the International Society on Thrombosis and Haemostasis) (18), and intracranial hemorrhage. Hazard ratios for edoxaban and warfarin with 95% confidence intervals were determined using Cox proportional hazards models with treatment as the only covariate. Cumulative incidence curves for the attainment of a therapeutic INR ≥2.0 were constructed using the Kaplan-Meier approach and compared using the log-rank test. All analyses were performed with Stata version 12.1 (Stata Corp., College Station, Texas).

RESULTS

Of the 21,105 patients randomized into the ENGAGE AF-TIMI 48 trial, 13,642 (65%) were alive and still taking the blinded study drug at their end-of-trial visit. Baseline characteristics of all patients

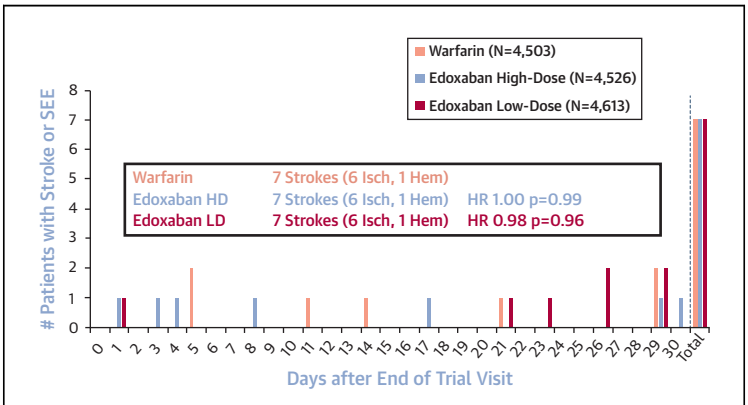


FIGURE 2 Stroke or SEE

Occurrence of stroke or systemic embolic during the 30-day transition period at the end of the trial. HD = high dose; Hem = hemorrhagic; HR = hazard ratio; Isch = ischemic; LD = low dose; SEE = systemic embolic event.

TABLE 2 Efficacy and Safety Outcomes

Outcome	Warfarin n (n = 4,503)	Warfarin %/yr (n = 4,503)	Edoxaban High Dose n (n = 4,526)	Edoxaban High Dose %/yr (n = 4,526)	Edoxaban High Dose Vs. Warfarin HR (95% CI)	Edoxaban High Dose Vs. Warfarin p Value	Edoxaban Low Dose n (n = 4,613)	Edoxaban Low Dose %/yr (n = 4,613)	Edoxaban Low Dose Vs. Warfarin HR (95% CI)	Edoxaban Low Dose Vs. Warfarin p Value
All patients										
Stroke/SEE	7	1.90	7*	1.89	1.00 (0.35–2.84)	0.99	7	1.85	0.98 (0.34–2.78)	0.96
Ischemic stroke	6	1.62	6	1.62	0.99 (0.32–3.08)	0.99	6	1.59	0.98 (0.31–3.03)	0.97
Hemorrhagic stroke	1	0.27	1	0.27	0.99 (0.06–15.91)	0.99	1	0.26	0.98 (0.06–15.61)	0.99
Major bleed	11	2.98	10†	2.69	0.90 (0.38–2.13)	0.82	18	4.76	1.60 (0.75–3.38)	0.22
ICH	2	0.54	1	0.27	0.50 (0.05–5.49)	0.56	2	0.53	0.98 (0.14–6.93)	0.98
All-cause mortality	7	1.89	8‡	2.15	1.14 (0.41–3.14)	0.80	10§	2.64	1.39 (0.53–3.66)	0.50
	(n = 3,147)		(n = 3,050)				(n = 3,107)			
Transitioned to VKA										
Stroke/SEE	5	1.94	4	1.60	0.83 (0.22–3.07)	0.78	4	1.57	0.81 (0.22–3.02)	0.75
Major bleed	7	2.71	7	2.80	1.03 (0.36–2.94)	0.95	10	3.93	1.45 (0.55–3.80)	0.45
All-cause mortality	5	1.94	5	2.00	1.03 (0.30–3.56)	0.96	7	2.74	1.42 (0.45–4.47)	0.55
	(n = 1,328)		(n = 1,445)				(n = 1,485)			
Transitioned to NOAC										
Stroke/SEE	2	1.84	2	1.69	0.92 (0.13–6.52)	0.93	3	2.46	1.34 (0.22–8.03)	0.75
Major bleed	4	3.68	2	1.69	0.46 (0.08–2.51)	0.36	8	6.57	1.79 (0.54–5.93)	0.34
All-cause mortality	2	1.84	2	1.69	0.92 (0.13–6.52)	0.93	2	1.64	0.89 (0.13–6.34)	0.91

*1 patient transitioned to no antithrombotic agent had an ischemic stroke. †1 patient transitioned to antiplatelet therapy had a major bleed. ‡1 patient transitioned to no antithrombotic agent died. §One patient transitioned to no antithrombotic agent died.

CI = confidence interval; HR = hazard ratio; ICH = intracranial hemorrhage; NOAC = new oral anticoagulant; SEE = systemic embolic event; VKA = vitamin K antagonist.

randomized and those on the blinded study drug (warfarin or edoxaban) at the end of the trial are shown in Table 1. Patients completing the trial on the blinded study drug were slightly younger and less likely to have received a reduced dose of the blinded study drug. Characteristics were balanced between treatment groups in patients on the study drug at the end of the trial.

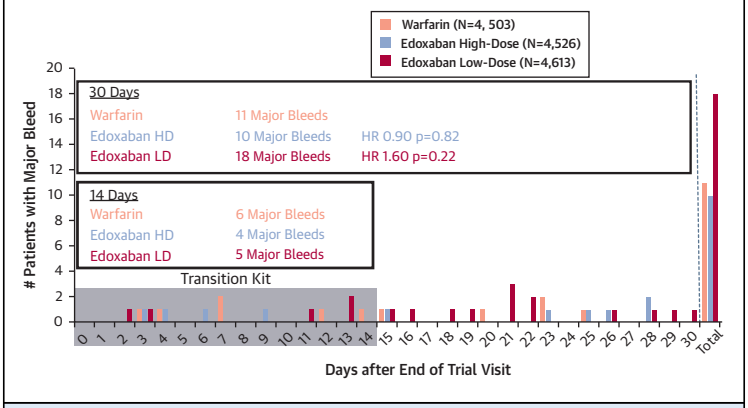


FIGURE 3 Bleeding Events

Occurrence of major bleeding during the 30-day transition period at the end of the trial. Abbreviations as in Figure 2.

TRANSITION: ALL PATIENTS. At the end of the trial, 9,304 (68.2%) of the 13,642 patients on the blinded study drug were transitioned to open-label VKA (Fig. 1). Of these, 6,702 (72%) had not been on a reduced dose of edoxaban or matching placebo at the end of the trial and were allocated to 30 mg edoxaban or matching placebo, in addition to maintenance dose, open-label VKA. The remaining 2,579 (27.7%) patients had been on a reduced dose of study drug and received a transition kit that contained 15 mg edoxaban or matching placebo. There were 4,258 (31.2%) patients who were transitioned to an open-label NOAC with a nearly even distribution between dabigatran (n = 2,140) and 1 of the 2 factor Xa inhibitors (rivaroxaban or apixaban) (n = 2,118). There were 80 patients (0.6%) who were transitioned to antiplatelet (n = 33) or no antithrombotic therapy (n = 47).

Figure 2 shows the distribution of the 21 strokes that occurred during the 30 days after the end of the trial (there were no SEEs). The strokes were evenly distributed across the 3 randomized

treatment arms: warfarin 7 events (1.90%/year), edoxaban high dose 7 events (1.89%/year), and edoxaban low dose 7 events (1.85%/year) (Table 2). Six of the 7 strokes in each group were ischemic. Major bleeding was also similar across the 3 randomized treatment arms during the 30-day end-of-study transition period (Fig. 3): warfarin 11 events (2.98%/year), edoxaban high dose 10 events (2.69%/year), and edoxaban low dose 18 events (4.76%/year) (Table 2). Major bleeding was also similar from days 1 to 14 when a transition kit and open-label VKA were given together (warfarin 6 events, edoxaban high dose 4 events, edoxaban low dose 5 events) (Fig. 3). During the 30-day period after the end of the study, there were 25 deaths balanced across the 3 treatment arms: warfarin 7 (1.89%/year), edoxaban high dose 8 (2.15%/year), edoxaban low dose 10 (2.64%/year) (Table 2).

TRANSITION OF PATIENTS TO OPEN-LABEL VKA. The results were consistent regardless of the open-label anticoagulant selected for transition (Table 2). Patients transitioned to an open-label VKA had similar rates across the 3 randomized treatment arms of stroke (warfarin 5 events [1.94%/year], edoxaban high dose 4 events [1.60%/year], edoxaban low dose 4 events [1.57%/year]), bleeding (warfarin 7 events [2.71%/year], edoxaban high dose 7 events [2.80%/year], edoxaban low dose 10 events [3.93%/year]), and all-cause mortality (warfarin 5 events [1.94%/year], edoxaban high dose 5 events [2.00%/year], edoxaban low dose 7 events [2.74%/year]).

The cumulative proportions of patients with at least 1 INR ≥2 in the first 30 days post-transition to open-label VKA are shown in Figure 4. In patients transitioned to an open-label VKA, 99.4%, 98.7%, and 98.9% of patients had at least 1 INR ≥2 in the warfarin, edoxaban high- and low-dose groups, respectively, by day 30 after the end of the study. By day 14, the last potential day of transition kit use, 96.6%, 84.9%, and 85.8% of patients had at least 1 INR ≥2 in the warfarin, edoxaban high-dose, and low-dose groups, respectively. The median time to an INR ≥2 was 9 days (interquartile range: 7 to 12 days) in the high- and low-dose edoxaban groups. In the warfarin group, 83% of patients had an INR ≥2 at the start of the transition.

TRANSITION OF PATIENTS TO OPEN-LABEL NOAC. In the 4,258 (31.2%) patients transitioned to NOACs, there were no significant differences in the rates of stroke for patients in the 3 groups: warfarin 2 events (1.84%/year), edoxaban high-dose 2 events (1.69%/year), edoxaban low-dose 3 events (2.46%/year) (Table 2). There were similar rates of major bleeding (warfarin 4 events [3.68%/year], edoxaban high-dose 2 events [1.69%/year], edoxaban low-dose 8 events [6.57%/year], and all-cause mortality (warfarin 2 events [1.84%/year], edoxaban high dose 2 events [1.69%/year], edoxaban low dose 2 events [1.64%/year]) across the 3 treatment groups.

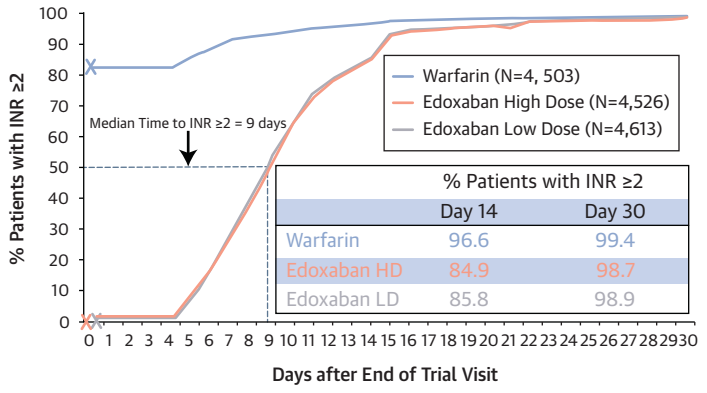


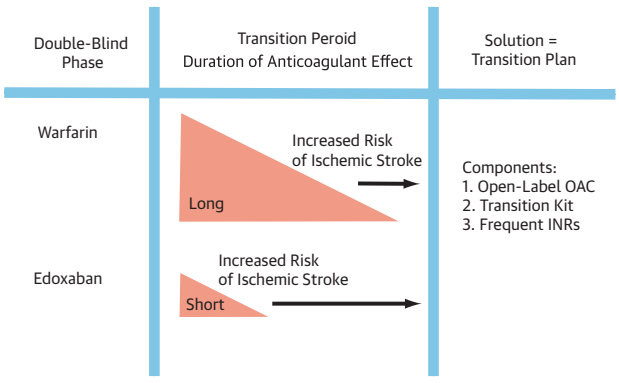
FIGURE 4 Cumulative Proportion of Patients Transitioned to Open-Label Vitamin K Anticoagulant With at Least 1 INR ≥2 Within 30 Days From End of Study

The **X** at day 0 represents the percentage of patients with an international normalized ratio (INR) ≥2 at the end-of-trial visit. Patients initially assigned edoxaban, who did not yet have an INR measured after the end-of-trial visit were assumed to have an INR <2.0 during the days between the last study visit and the first post-study INR measurement on day 4 or later. Abbreviations as in Figure 2.

DISCUSSION

Warfarin and other VKAs were the only oral anticoagulants available for stroke prevention for more than a half a century. Since 2009, NOACs have been demonstrated to be at least as effective and safe as warfarin in 4 large phase 3 trials in patients with AF, (7-10), but an excess of both thrombotic and bleeding events occurred in patients randomized to NOACs in the 2 previous trials, ROCKET AF (11) and ARISTOTLE (12), that reported outcomes in the month following the end of the trial as patients were transitioned to open-label VKA. Learning from these experiences, we developed a transition plan for the ENGAGE AF-TIMI 48 trial, which protected patients from excess stroke and bleeding as they were transitioned from warfarin or edoxaban to 1 of 3 open-label anticoagulants (Central Illustration).

The most likely explanation for the excess of ischemic events observed in earlier trials is the delay



CENTRAL ILLUSTRATION Key Components of the End-of-Trial Transition

At the end of 2 previous trials, an excess of stroke and bleeding was observed in patients with AF randomized to a new oral anticoagulant (NOAC) who transitioned to a vitamin K antagonist (VKA). In the ENAGE AF-TIMI 48 trial, a transition plan was developed to protect patients transitioning to open-label VKA or an NOAC at the trial's end by minimizing both the risk of ischemic stroke due to inadequate anticoagulation and the risk of bleeding with excessive anticoagulation while maintaining the integrity of the blinding to the treatment allocation. The end-of-trial transition plan consisted of 4 key components: 1) selection of the oral anticoagulant (VKA or an NOAC) by the treating physician and patient; 2) a 14-day transition kit of modified-dose edoxaban for patients randomized to edoxaban or matching placebo for patients randomized to warfarin; 3) early and frequent international normalized ratio (INR) testing (≥3 tests during the first 2 weeks); and 4) use of a VKA titration algorithm.

in achieving a therapeutic INR in patients who had been randomized to an NOAC and who were then transitioned to an open-label VKA, compared with patients who had been randomized to warfarin and who were then transitioned to open-label VKA. When patients discontinue anticoagulant therapy, the risk of stroke rises once the anticoagulant effect wears off: in 24 to 48 h with NOACs and in 3 to 5 days with warfarin. In the case of 2 prior trials with factor Xa inhibitors (11,12) at the end of the trial when study medication was discontinued, a majority of the patients randomized to warfarin had a therapeutic INR. The lapse in therapeutic anticoagulation levels was greater in patients transitioning from an NOAC to an open-label VKA before they achieved a therapeutic INR than patients who were transitioned from warfarin to open-label VKA. In the ROCKET AF trial, the median time to first therapeutic INR ≥2 on open-label VKA was 13 days in the rivaroxaban group (11). By 30 days after the end of the trial, 83% of the warfarin group had ≥1 therapeutic INR value compared with only 52% of the rivaroxaban group. The 2-day transition period with apixaban/matching placebo in the ARISTOTLE trial was likely too short in patients transitioning from apixaban to open-label VKA to cover the period while the INR was subtherapeutic (INR data not published) (12).

The end-of-trial transition plan for the ENGAGE AF-TIMI 48 trial addressed several of the limitations that arose in prior studies. The period of overlap with edoxaban/matching placebo transition kit was extended up to 14 days, so that patients who had been randomized to edoxaban would have a sufficient period of full anticoagulant protection with edoxaban while their dose of open-label VKA was titrated to achieve a therapeutic INR. But this is helpful only if patients achieve a therapeutic INR within 2 weeks. A critical feature of the ENGAGE AF-TIMI 48 transition plan was early and frequent INR testing with use of a dose titration algorithm to ensure that the majority of patients randomized to open-label VKA achieved a therapeutic INR before lapse of their coverage with the transition kit. We believe that aggressive and standardized guidance to promote rapid titration of VKA dose to achieve a therapeutic level enabled 85% of patients randomized to edoxaban and transitioned to open-label VKA to achieve at least 1 therapeutic INR within 14 days after the end of the trial and ~99% by day 30. The ROCKET AF investigators provide additional evidence supporting the importance of frequent INR testing. Physicians managed patients using local standards, and the number of INR measurements during the transition was variable. Geographic regions with more frequent INR monitoring had fewer events (11).

Aggressive monitoring and titration of VKA therapy is also critical to protect patients from the complications of serious bleeding. The transition strategy in the ENGAGE AF-TIMI 48 trial protected patients from the excess bleeding that was observed in the earlier trials even though anticoagulation with an edoxaban transition kit overlapped with open-label VKA extended for up to 14 days. The dose modification in the transition kit (30 mg once daily for patients who had not been dose reduced at the end-of-trial visit and 15 mg once daily for patients who had been dose reduced at the end-of-trial visit, regardless of randomized drug assignment) likely helped mitigate the bleeding risk with overlapping anticoagulation. Whether simply continuing all patients on the dose of edoxaban they were on during the trial would have resulted in an excess of bleeding is unknown.

In addition to the protection of patients transitioning to open-label VKA, 4,258 patients were transitioned to an open-label NOAC from both warfarin (n = 1,328) and edoxaban (n = 2,930). There was no excess of stroke or bleeding observed, reassuring both clinicians and patients that the transition to an NOAC can be accomplished safely.

VKAs are effective as long as a therapeutic INR can be rapidly reached and maintained. Results of our analyses support that structured and standardized guidance accompanied by frequent monitoring are required for VKAs to fulfill their promise, which is protection against ischemic events while minimizing the risk of serious bleeding. The challenge in achieving this balance with the resources available in routine clinical practice has limited our ability to improve the adoption and compliance of VKAs in the expanding population of patients with AF at risk for stroke.

CONCLUSIONS

The transition plan in the ENGAGE AF-TIMI 48 trial protected patients from an excess of thrombotic and bleeding events, and its use may provide reassurance that in clinical practice patients can be safely transitioned between a broad range of oral anticoagulants.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: AF predisposes patients to an increased risk of embolic stroke. Warfarin and other VKAs are highly effective in preventing stroke, but limited by their narrow therapeutic window and the inconveniences imposed by the need for coagulation monitoring and frequent dose adjustments.

COMPETENCY IN MEDICAL KNOWLEDGE 2: Four NOACs that inhibit thrombin (factor II) or activated factor X (factor Xa) are at least as effective and safe as warfarin for preventing stroke in patients with AF but at the end of previous double-blind randomized trials of NOACs there was an excess of both stroke and bleeding events when patients were transitioned to open-label anticoagulation.

COMPETENCY IN PATIENT CARE: Transitioning from 1 anticoagulant to another is a high-risk period for patients. The transition plan in the ENGAGE AF-TIMI 48 trial minimized the risks of stroke due to inadequate anticoagulation and bleeding from excessive anticoagulation during this critical period, providing reassurance that patients can be safely transitioned between oral anticoagulants.

TRANSLATIONAL OUTLOOK: More research is needed to determine the optimum strategies and guidance for patients who must change from 1 anticoagulant to another before and after procedures, when side effects occur, changes in insurance coverage require selection of an alternative drug or other clinical developments force therapeutic adjustment.

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KEY WORDS anticoagulation, atrial fibrillation, edoxaban, factor Xa inhibitor, new oral anticoagulants, vitamin K antagonist

APPENDIX For supplemental tables, please see the online version of this article.