Network Meta-Analysis of Relative Efficacy and Safety of Edoxaban Versus Other Novel Oral Anticoagulants (NOACs) Among Atrial Fibrillation Patients With $CHADS_2$ Score ≥ 2

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BACKGROUND

- Treatment guidelines recommend the use of oral anticoagulation therapy for the prevention of stroke in patients with nonvalvular atrial fibrillation (NVAF) and a $CHADS_2$ score ≥ 2.
- The efficacy and safety of novel oral anticoagulants (NOACs) versus warfarin have been evaluated in four pivotal large-scale phase 3 randomized controlled trials, with notable differences in study designs and patient characteristics: RE-LY (dabigatran),[1] ROCKET-AF (rivaroxaban),[2] ARISTOTLE (apixaban),[3] and ENGAGE AF-TIMI 48 (edoxaban).[4]
- In the absence of head-to-head trials comparing the efficacy and safety of NOACs, a network meta-analysis (indirect treatment comparison) has been used to assess the relative efficacy and safety of alternative NOACs for stroke prevention in patients with NVAF.[5-7]

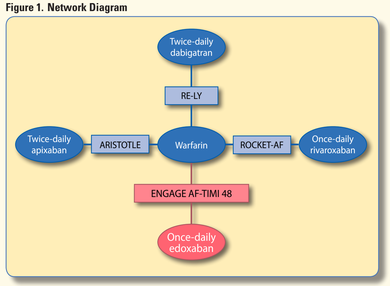
OBJECTIVE

- To assess the relative efficacy and safety of edoxaban versus other NOACs after adjusting for differences in baseline $CHADS_2$ score and duration of study follow-up across the four pivotal trials in patients with NVAF, using a network meta-analysis.

METHODS

- We systematically searched the PubMed, Embase, and Cochrane databases, as well as conference abstracts and clinical trial registers, to identify phase 3 randomized controlled trials evaluating NOACs for prevention of stroke in patients with NVAF and their associated publications.[8,9]
- A network meta-analysis was performed using data from the RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE AF-TIMI 48 studies, with warfarin as a common comparator (Figure 1).

Figure 1. Network Diagram



- Table 1 summarizes the study design and baseline characteristics of patients enrolled in the four pivotal trials.
  - ROCKET-AF and ENGAGE AF-TIMI 48 enrolled only patients with $CHADS_2$ score ≥ 2; thus, these patients had a higher mean $CHADS_2$ score than those in RE-LY and ARISTOTLE.
  - ENGAGE AF-TIMI 48 had the longest length of study follow-up, almost 1 year longer than ROCKET-AF and ARISTOTLE.
- Our study evaluated the following primary efficacy and safety endpoints:
  - Composite of stroke/systemic embolism
  - Major bleeding
- Additionally, we evaluated the following secondary endpoints, depending on data availability:
  - Composite of major bleeding and clinically relevant nonmajor (CRNM) bleeding
  - Ischemic stroke
  - Hemorrhagic stroke
  - Systemic embolism
  - All-cause mortality
  - Cardiovascular mortality
  - Myocardial infarction
  - Intracranial hemorrhage
  - Gastrointestinal bleeding
  - CRNM bleeding
  - Fatal bleeding
- To adjust for differences in $CHADS_2$ score across the trials, annualized event rates of edoxaban versus other NOACs were compared using data among patients with $CHADS_2$ score ≥ 2.
  - For each outcome, a mixed Poisson regression model with treatment as fixed effect and study as random effect was developed to adjust for differences in length of follow-up. Risk ratios and 95% confidence intervals (CIs) were reported.
- All analyses were conducted using SAS software version 9.3.

Table 1.
Summary of Baseline Characteristics of Patients in Randomized Controlled Trials

Characteristic	RE-LY (Twice-Daily Dabigatran)	ROCKET-AF (Once-Daily Rivaroxaban)	ARISTOTLE (Twice-Daily Apixaban)	ENGAGE AF-TIMI 48 (Once-Daily Edoxaban)
Total no. of patients	18,113	14,264	18,201	21,105
Trial design	Open label	Double blinded	Double blinded	Double blinded
Years of follow-up, median	2.0	1.9	1.8	2.8
Male	63.2% (D), 63.3% (W)	60.3% (R) 60.3% (W)	64.5% (A), 65.0% (W)	62.1% (E), 62.4% (W)
$CHADS_2$ score				
Mean	2.2 (D), 2.1 (W)	3.5 (R), 3.5 (W)	2.1 (A), 2.1 (W)	2.8 (E), 2.8 (W)
≥ 2	67.8% (D), 69.1% (W)	100%	66%	100%
≥ 3	32.6% (D), 32.1% (W)	87%	30.2%	53.4% (E), 52.6% (W)
Comorbidity				
Previous stroke or transient ischemic attack	20.3% (D), 19.8% (W)	54.9% (R), 54.6% (W)	19.2% (A), 19.7% (W)	28.1% (E), 28% (W)
Diabetes	23% (D), 23% (W)	40% (R), 40% (W)	25% (A), 25% (W)	36% (E), 36% (W)
Hypertension	79% (D), 79% (W)	90% (R), 91% (W)	87% (A), 88% (W)	94% (E), 94% (W)
Heart failure	31.8% (D), 31.9% (W)	62.6% (R), 62.3% (W)	35.5% (A), 35.4% (W)	58.2% (E), 58% (W)
Mean cTTR	64.0%	55.0%	62.2%	64.9%

A = apixaban; $CHADS_2$ = stroke risk factor scoring system in which 1 point is given for history of congestive heart failure, hypertension, age > 75 years, and diabetes, and 2 points are given for history of stroke or transient ischemic attack; cTTR = center time in therapeutic range; D = dabigatran; E = edoxaban; R = rivaroxaban; W = warfarin.

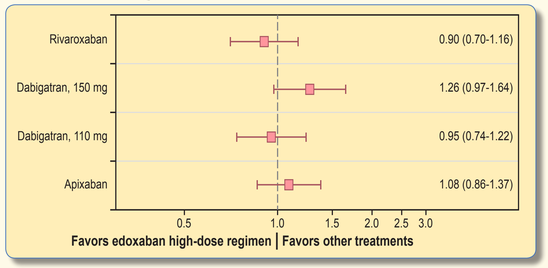
RESULTS

Efficacy Endpoints

Primary Efficacy Endpoint

- Among patients with $CHADS_2$ score ≥ 2, for the primary efficacy endpoint (composite of stroke/systemic embolism), high-dose edoxaban (60 mg) regimen had a risk ratio similar to apixaban, dabigatran 150 mg, dabigatran 110 mg, and rivaroxaban (Figure 2).
- Low-dose edoxaban (30 mg) regimen had a significantly higher risk of stroke/systemic embolism than apixaban (rate ratio [RR], 1.41; 95% CI, 1.12-1.77) and dabigatran 150 mg (RR, 1.64; 95% CI, 1.26-2.13).

Figure 2. Risk Ratios and 95% CIs on Composite of Stroke/Systemic Embolism for High-Dose Edoxaban Versus Other NOACs in Patients With $CHADS_2$ Score ≥ 2 at Baseline



Key Secondary Efficacy Endpoints

- Table 2 presents a comparison of high- and low-dose edoxaban regimens versus other NOACs for various key secondary endpoints, based on available published data.
  - No significant differences in ischemic stroke risk were found among high-dose edoxaban regimen, apixaban, and rivaroxaban treatment groups.
  - Compared with rivaroxaban, the risk ratio of hemorrhagic stroke with high-dose edoxaban regimen was similar.
  - No significant differences were found in all-cause mortality and cardiovascular mortality between high- and low-dose edoxaban regimens and other NOACs for which data were available.
  - No significant differences were found between high-dose edoxaban regimen and rivaroxaban, for myocardial infarction.

Table 2. Key Secondary Efficacy Endpoints From Network Meta-Analysis: RR (95% CI) for High- and Low-Dose Edoxaban Versus Other NOACs in Patients With $CHADS_2$ Score ≥ 2 at Baseline

Secondary Efficacy Endpoint	Relative Risk Ratio (95% CI)			
	Once-Daily Rivaroxaban	Twice-Daily Apixaban	Twice-Daily Dabigatran, 110 mg	Twice-Daily Dabigatran , 150 mg
Once-daily high-dose edoxaban (60 mg/30 mg dose reduced)				
Ischemic stroke	0.95 (0.73-1.24)	1.09 (0.81-1.48)	N/A	N/A
Hemorrhagic stroke	0.87 (0.56-1.35)	N/A	N/A	N/A
Systemic embolism	0.57 (0.25-1.27)	N/A	N/A	N/A
All-cause mortality	0.95 (0.83-1.08)[a]	1.01 (0.87-1.16)	0.95 (0.81-1.10)	0.94 (0.81-1.09)
Cardiovascular mortality	0.99 (0.78-1.25)[a]	N/A	0.93 (0.80-1.08)	0.96 (0.82-1.12)
Myocardial infarction	1.05 (0.72-1.51)[a]	1.15 (0.86-1.55)	N/A	N/A
Once-daily low-dose edoxaban (30 mg/15 mg dose reduced)				
Ischemic stroke	1.34 (1.04-1.74)	1.55 (1.15-2.09)	N/A	N/A
Hemorrhagic stroke	0.53 (0.33-0.87)	N/A	N/A	N/A
Systemic embolism	1.07 (0.51-2.23)	N/A	N/A	N/A
All-cause mortality	0.90 (0.79-1.03)[a]	0.96 (0.83-1.10)	0.90 (0.77-1.05)	0.90 (0.77-1.04)
Cardiovascular mortality	0.97 (0.77-1.24)[a]	N/A	0.92 (0.79-1.07)	0.95 (0.81-1.10)
Myocardial infarction	1.35 (0.94-1.93)[a]	1.47 (1.10-1.95)	N/A	N/A

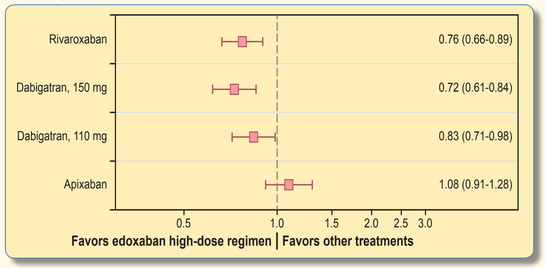
N/A = not available.
[a] Data from the safety, on-treatment population were used for rivaroxaban due to data availability.

Safety Endpoints

Primary Safety Endpoint

- Among patients with $CHADS_2$ score ≥ 2, for the primary safety endpoint (major bleeding), high-dose edoxaban regimen had a significantly lower major bleeding rate than rivaroxaban, dabigatran 150 mg, and dabigatran 110 mg (Figure 3), and a similar bleeding rate to apixaban.
- Low-dose edoxaban regimen had a significantly lower rate of major bleeding than all other NOACs, with an RR of 0.63 (95% CI, 0.52-0.76) versus apixaban, 0.42 (95% CI, 0.35-0.50) versus dabigatran 150 mg, 0.49 (95% CI, 0.41-0.59) versus dabigatran 110 mg, and 0.45 (95% CI, 0.38-0.53) versus rivaroxaban.

Figure 3. Risk Ratios and 95% CIs on Major Bleeding for High-Dose Edoxaban Versus Other NOACs in Patients With $CHADS_2$ Score ≥ 2 at Baseline



Key Secondary Safety Endpoints

- For the composite of major bleeding and CRNM bleeding, which was the primary safety endpoint in ROCKET-AF, high-dose (RR, 0.81; 95% CI, 0.72-0.90) and low-dose (RR, 0.58; 95% CI, 0.52-0.65) edoxaban regimens had significantly lower rates than rivaroxaban. No data for dabigatran and apixaban were available for major and CRNM bleeding in patients with $CHADS_2$ score ≥ 2.
- Table 3 presents comparisons for other key secondary safety endpoints.
  - No significant differences in the risk of intracranial hemorrhage were found among the NOACs, except low-dose edoxaban regimen had significantly lower risk than rivaroxaban..
  - Compared with rivaroxaban, both high- and low-dose edoxaban regimens had significantly lower risks of major gastrointestinal bleeding.
  - For the rest of the safety endpoints in Table 3, the comparisons versus apixaban and dabigatran were not conducted because data were not available.

Table 3. Key Secondary Safety Endpoints From Network Meta-Analysis: RR (95% CI) for High- and Low-Dose Edoxaban Versus Other NOACs in Patients With $CHADS_2$ Score ≥ 2 at Baseline

Secondary Safety Endpoint	Relative Risk Ratio (95% CI)			
	Once-Daily Rivaroxaban	Twice-Daily Apixaban	Twice-Daily Dabigatran, 110 mg	Twice-Daily Dabigatran , 150 mg
Once-daily high-dose edoxaban (60 mg/30 mg dose reduced)				
Intracranial hemorrhage	0.76 (0.52-1.10)	1.06 (0.69-1.62)	1.63 (0.96-2.76)	1.02 (0.65-1.59)
Major gastrointestinal bleeding	0.75 (0.63-0.91)	N/A	N/A	N/A
CRNM bleeding	0.80 (0.71-0.90)	N/A	N/A	N/A
Fatal bleeding	1.22 (0.68-2.17)	N/A	N/A	N/A
Once-daily low-dose edoxaban (30 mg/15 mg dose reduced)				
Intracranial hemorrhage	0.50 (0.33-0.77)	0.71 (0.45-1.12)	1.09 (0.62-1.90)	0.68 (0.42-1.10)
Major gastrointestinal bleeding	0.41 (0.33-0.51)	N/A	N/A	N/A
CRNM bleeding	0.61 (0.54-0.69)	N/A	N/A	N/A
Fatal bleeding	0.75 (0.40-1.41)	N/A	N/A	N/A

N/A = not available.

LIMITATIONS

- Although mixed Poisson models allow adjustment of varied study follow-up periods across the pivotal trials, this method assumes the risk of events to be constant over time; however, chance of events may vary during the exposure time.
- A comprehensive evaluation of the relative efficacy and safety of edoxaban versus dabigatran and apixaban was not possible for many secondary endpoints, because published data for patients with $CHADS_2$ score ≥ 2 were not available from the RE-LY and ARISTOTLE trials.
- Although we sought to reduce heterogeneity bias across the study by limiting comparison of data from patients with $CHADS_2$ score ≥ 2 in each of the four clinical trials, in the absence of patient-level data, we could not control for other important differences, such as warfarin cTTR and the use of open-label versus double-blind study design across the clinical trials. In addition, due to the small number of studies and the lack of repeated pairs of treatment, we were unable to perform a heterogeneity test. Therefore, heterogeneity bias cannot be ruled out.

CONCLUSIONS

- Among patients with NVAF and $CHADS_2$ score ≥ 2, a once-daily high-dose edoxaban (60 mg/30 mg dose reduced) regimen has similar efficacy in reducing the risk of stroke and systemic embolism to other NOACs and has a significantly lower risk of major bleeding compared with rivaroxaban and dabigatran 150 mg and dabigatran 110 mg. The risk of major bleeding associated with a once-daily high-dose edoxaban (60 mg/30 mg dose reduced) regimen was similar to that associated with apixaban.

DISCLOSURE

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