European Heart Journal (2015) **36**, 1470–1477
doi:10.1093/eurheartj/ehv014

Edoxaban vs. warfarin in vitamin K antagonist experienced and naive patients with atrial fibrillation†

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Received 26 August 2014; revised 5 December 2014; accepted 14 January 2015; online publish-ahead-of-print 16 February 2015

See page 1431 for the editorial comment on this article (doi:10.1093/eurheartj/ehv032)

Aims Edoxaban is an oral, once-daily factor Xa inhibitor that is non-inferior to well-managed warfarin in patients with atrial fibrillation (AF) for the prevention of stroke and systemic embolic events (SEEs). We examined the efficacy and safety of edoxaban vs. warfarin in patients who were vitamin K antagonist (VKA) naive or experienced.

Methods and results ENGAGE AF-TIMI 48 randomized 21 105 patients with AF at moderate-to-high risk of stroke to once-daily edoxaban vs. warfarin. Subjects were followed for a median of 2.8 years. The primary efficacy endpoint was stroke or SEE. As a pre-specified subgroup, we analysed outcomes for those with or without prior VKA experience (>60 consecutive days). Higher-dose edoxaban significantly reduced the risk of stroke or SEE in patients who were VKA naive [hazard ratio (HR) 0.71, 95% confidence interval (CI) 0.56–0.90] and was similar to warfarin in the VKA experienced (HR 1.01, 95% CI 0.82–1.24; *P* interaction = 0.028). Lower-dose edoxaban was similar to warfarin for stroke or SEE prevention in patients who were VKA naive (HR 0.92, 95% CI 0.73–1.15), but was inferior to warfarin in those who were VKA experienced (HR 1.31, 95% 1.08–1.60; *P* interaction = 0.019). Both higher-dose and lower-dose edoxaban regimens significantly reduced the risk of major bleeding regardless of prior VKA experience (*P* interaction = 0.90 and 0.71, respectively).

Conclusion In patients with AF, edoxaban appeared to demonstrate greater efficacy compared with warfarin in patients who were VKA naive than VKA experienced. Edoxaban significantly reduced major bleeding compared with warfarin regardless of prior VKA exposure.

Keywords Edoxaban • Warfarin • Atrial fibrillation • Novel oral anticoagulant

Introduction

Edoxaban is an oral direct factor Xa inhibitor that is non-inferior to well-managed warfarin for the prevention of stroke or systemic embolic events (SEEs) in individuals with atrial fibrillation (AF).[1] In addition to the prevention of thrombo-embolic events, edoxaban has been shown to significantly reduce the risk of bleeding and cardiovascular death when compared with warfarin.[1] Registry data now suggest that the majority of patients with AF who are initiating novel oral anticoagulant (NOAC) therapy do not have a prior history of vitamin K antagonist (VKA) exposure.[2,3] In turn, prior studies have shown that individuals without prior VKA exposure have a higher incidence of stroke when initiated on anticoagulant therapy as compared with those who are VKA experienced.[4] Therefore, the efficacy and safety of NOAC therapy in VKA naive patients are of critical clinical interest as therapeutic decisions and patients' acceptance to initiate VKAs are highly influenced by the high incidence of clinical events and bleeding during the VKA initial titration.[5]

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† Since submission of this paper, the higher dose of edoxaban has been approved for the prevention of stroke or systemic embolism in patients with atrial fibrillation by the U.S. Food and Drug administration, and regulatory authorities in Japan.

Further, it remains unclear whether patients who are currently managed on a VKA derive comparable efficacy and safety when they transition to a NOAC. To address these issues, we examined the efficacy and safety of edoxaban vs. warfarin in patients with AF stratified by prior VKA exposure in the ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48) trial.[1]

Methods

Study population and procedures

The design and results of the ENGAGE AF-TIMI 48 trial have been reported previously.[1,6] In brief, ENGAGE AF-TIMI 48 was a phase 3 multinational, double-blind, double-dummy, non-inferiority trial that enrolled 21 105 patients with AF at moderate-to-high risk of stroke and randomized them to higher-dose edoxaban (60 mg once daily), lower-dose edoxaban (30 mg once daily), or warfarin. The edoxaban dose was reduced by 50% for patients with a body weight $\leq$60 kg, estimated creatinine clearance 30–50 mL/min, or in those that required concomitant use of a potent P-glycoprotein inhibitor (verapamil, quinidine, or dronedarone). After dose reduction, patients remained in the randomized dose arm to which they were originally assigned. Eligibility criteria included AF documented by means of an electrical recording within 12 months of enrolment and a $CHADS_2$ score $\geq$2.

Endpoints

The primary efficacy endpoint of the ENGAGE AF-TIMI 48 trial was the first occurrence of stroke or SEE. Key secondary endpoints included the composite of stroke, SEE, and cardiovascular mortality or all-cause mortality, as well as each component separately. The primary safety endpoint was adapted according to the International Society on Thrombosis and Haemostasis definition of major bleeding.[6] A blinded and independent clinical events committee adjudicated all deaths, as well as suspected cerebrovascular events, SEEs, myocardial infarctions, bleeding, and hepatic events.

Definition of vitamin K antagonist experience

For the current analysis, subjects were divided into subgroups on the basis of whether they were VKA naive or VKA experienced, as pre-specified in the study protocol[1] and statistical analysis plan. Vitamin K antagonist experience was defined as >60 days of continuous anticoagulation with a VKA at any time prior to randomization as captured in the case-report form. As a sensitivity analysis, the analysis was also conducted according to whether or not subjects were receiving a VKA at the time of randomization, as well as by whether or not they had any history of prior VKA exposure (for any duration of time). An additional sensitivity analysis was conducted on the basis of whether patients did or did not have an indication for edoxaban dose reduction regardless of treatment arm.

Statistical analysis

Baseline characteristics are presented as medians (interquartile ranges) for continuous variables and frequencies for categorical variables. Baseline characteristics were compared with the Wilcoxon rank-sum tests for continuous variables and χ^2 tests for categorical variables.

Efficacy analyses were conducted with a Cox proportional-hazards model that included treatment arm and the two randomization stratification factors ($CHADS_2$ score and the need for a 50% edoxaban dose reduction) and restricted on the basis of prior VKA exposure. Effect modification was assessed by including an interaction term in the model.

For the current analysis, the primary efficacy analysis was conducted in the intention-to-treat study population, including all clinical endpoints that occurred from randomization to the end-of-treatment period in all enrolled subjects regardless of whether or not subjects were on study drug, as pre-specified in the analysis plan. A sensitivity analysis was conducted that was restricted to the modified intention-to-treat population while on-treatment [defined as the period between administration of the first dose of the study drug and either 3 days after the receipt of the last dose or the end of the double-blind therapy (whichever came first), with interval censoring of events during study-drug interruptions that lasted more than 3 days]. Safety analyses were restricted to those patients who had received at least one dose of study drug. All tests were two-sided with a P-value of <0.05 considered to be significant. The TIMI Study Group has an independent copy of the trial database and conducted the current analysis. Analyses were performed with use of Stata/SE version 12.1 (Stata Corp., College Station, TX, USA).

Results

Of the 21 105 subjects enrolled in the trial, 8663 (41%) were VKA naive ($\leq$60 days of prior continuous VKA exposure) and 12 441 (59%) were VKA experienced prior to randomization. Subjects who were VKA naive were more likely to be younger, female, Asian, to have a history of hypertension or heart failure, were more likely to be on aspirin at randomization, and had a lower body mass index than those who were VKA experienced. Subjects who were VKA naive also were more likely to have an edoxaban dose reduction at baseline due to a lower creatinine clearance (30–50 mL/min) and a lower weight ($\leq$60 kg; *Table 1*). In contrast, VKA experienced subjects were more likely to be Caucasian and have a history of permanent AF, stroke or transient ischaemic attack, valvular disease, coronary artery disease, diabetes mellitus, hyperlipidaemia, and a $CHADS_2$ score >3 (*Table 1*).

Through long-term follow-up, the median percentage time in therapeutic range (TTR, INR 2–3) on warfarin was significantly lower for patients who were VKA naive (64.6%, IQR 51.1–74.4) than in those who were VKA experienced (70.8%, IQR 60.2–79.1%, $P < 0.001$). During the first 90 days (days 8–90), the median TTR was 43% for VKA naive patients and 59% in patients who were VKA experienced. At follow-up visits, VKA naive patients continued to have a higher frequency of aspirin use than those who were VKA experienced (27 vs. 19%, $P < 0.001$ at month 12).

In the total population, irrespective of treatment arm and without accounting for baseline differences, the aggregate annualized incidence rates for stroke or SEE (1.86% in VKA naive vs. 1.77% in VKA experienced, $P = 0.44$) and major bleeding (2.76% in VKA naive vs. 2.74% in VKA experienced, $P = 0.99$) were similar for patients who were VKA naive vs. VKA experienced. The aggregate annualized incidence of ischaemic stroke was 1.49% in patients who were VKA naive and 1.38% in patients who were VKA experienced ($P = 0.29$).

Efficacy outcomes

The higher-dose edoxaban regimen significantly reduced the risk of stroke or SEE in patients who were VKA naive [hazard ratio (HR) 0.71, 95% confidence interval (CI) 0.56–0.90] and was similar to warfarin in those who were VKA experienced (HR 1.01, 95% CI 0.82–1.24; P interaction = 0.028, *Figure 1*). A lower-dose edoxaban

Table 1 Baseline characteristics for those patients who were vitamin K antagonist naive (≤60 consecutive days of prior vitamin K antagonist exposure) vs. vitamin K antagonist experienced

Characteristic	VKA naive (*n* = 8663)	VKA experienced (*n* = 12 441)
Age [median (IQR), years]	71 (63–77)	72 (65–78)
Age ≥65 years	70.9%	76.1%
Male	57.9%	64.7%
White race	76.7%	83.8%
Body mass index [median (IQR), kg/m^2]	28 (25–32)	29 (26–33)
Current smoker	7.4%	7.3%
Region		
North America	13.0%	28.6%
Latin America	16.0%	10.3%
Western Europe	13.7%	16.5%
Eastern Europe	38.4%	30.7%
Asia, Japan, and South Africa	18.9%	14.0%
Type of atrial fibrillation		
Paroxysmal	31.9%	20.9%
Persistent	29.6%	18.5%
Permanent	38.4%	60.6%
Qualifying risk factor		
Age ≥75	38.0%	41.6%
Prior stroke or TIA	27.3%	29.0%
Prior heart failure	60.6%	55.2%
Diabetes mellitus	33.2%	38.2%
Hypertension	94.3%	93.1%
$CHADS_2$ score >3	21.8%	23.1%
Dose reduction at randomization	26.9%	24.3%
Due to Cr Cl 30–50 mL/min	19.5%	18.3%
Due to weight ≤60 kg	12.3%	8.4%
Due to verapamil or quinidine use	2.6%	3.6%
History of valvular heart disease	18.2%	23.0%
Medications at randomization		
Aspirin	41.7%	20.7%
Thienopyridine	3.3%	1.6%
Amiodarone	14.7%	9.8%
VKA use at randomization	36.7%	94.0%

All *P* values <0.001, except for current smoker ($P = 0.77$), prior stroke or TIA ($P = 0.01$), $CHADS_2$ score >3 ($P = 0.02$), and dose reduction at randomization due to creatinine clearance 30–50 mL/min ($P = 0.026$).
IQR, interquartile range; TIA, transient ischaemic attack; VKA, vitamin K antagonist; Cr Cl, creatinine clearance.

regimen had similar efficacy to warfarin in patients who were VKA naive (HR 0.92, 95% CI 0.73–1.15), whereas assignment to a lower-dose edoxaban regimen had a higher incidence of stroke or SEE in patients who were VKA experienced (HR 1.31, 95% CI 1.08–1.60; *P* interaction = 0.019; *Figures 2* and *3*). When individual components were examined, the greater efficacy of edoxaban in VKA naive subjects appeared to be explained by a ~60% higher incidence of ischaemic stroke in warfarin-treated patients who were VKA naive (1.60% per year) when compared with those who were VKA experienced (1.02% per year, $P < 0.001$; *Figures 1* and *2*).

There were similar directional signals towards greater reductions in cardiovascular and all-cause mortality with both doses of edoxaban as compared with warfarin in patients who were VKA naive, as compared with those who were VKA experienced; however, the differences between prior VKA use subgroups were not statistically significant and therefore consistent with the overall study results. The higher-dose edoxaban regimen had consistent effects on the risk of CV death [HR 0.79, 95% CI 0.67–0.94 (VKA naive); HR 0.93, 95% CI 0.79–1.09 (VKA experienced); *P* interaction = 0.19)] and all-cause mortality [HR 0.83, 95% CI 0.72–0.96 (VKA naive); HR 0.99, 95% CI 0.87–1.13 (VKA experienced); *P* interaction = 0.07)] regardless of prior VKA exposure (*Figure 1*). A consistent pattern was also observed with the lower-dose edoxaban regimen in regards to CV death [HR 0.81, 95% CI 0.69–0.96 (VKA naive); HR 0.89, 95% CI 0.76–1.05 (VKA experienced); *P* interaction = 0.45] and all-cause mortality [HR 0.82, 95% CI 0.71–0.95 (VKA naive); HR 0.91, 95% CI 0.80–1.04 (VKA experienced); *P* interaction = 0.30; *Figure 2*].

Safety outcomes

Both the higher-dose and lower-dose edoxaban regimens significantly reduced the risk of major bleeding when compared with warfarin regardless of whether subjects were VKA naive or VKA experienced (*Table 2*). Specifically, the higher-dose edoxaban regimen significantly reduced major bleeding by 20% (2.88 vs. 3.64% per year) in patients who were VKA naive and by 19% (2.85 vs. 3.54% per year) in those who were VKA experienced (*P* interaction = 0.90). The lower-dose edoxaban regimen significantly reduced major bleeding by 51% (1.80 vs. 3.64% per year) in patients who were VKA naive and by 48% (1.84 vs. 3.54% per year) in those who were VKA experienced (*P* interaction = 0.71). Similar findings were observed for other bleeding endpoints irrespective of whether patients were VKA naive or VKA experienced, including a significant reduction in intracranial haemorrhage with both higher-dose and lower-dose edoxaban regardless of prior VKA exposure (*Table 2*).

Composite and net clinical outcomes

The higher-dose edoxaban regimen significantly reduced the risk of the net clinical outcome of stroke or SEE, major bleeding, and all-cause death in those subjects who were VKA naive (HR 0.82, 95% CI 0.73–0.92) and was similar to warfarin in those who were VKA experienced [HR 0.95, 95% CI 0.86–1.05; *P* interaction (randomized treatment × VKA exposure) = 0.049]. The lower-dose edoxaban regimen significantly reduced the incidence of the same net clinical outcome in both VKA naive and VKA experienced subjects [23 and 11% relative risk reduction, respectively, *P* interaction (randomized treatment × VKA exposure) = 0.055; *Figure 4*], as compared with warfarin. Consistent qualitative results were observed for other secondary and net clinical outcomes (*Table 3*).

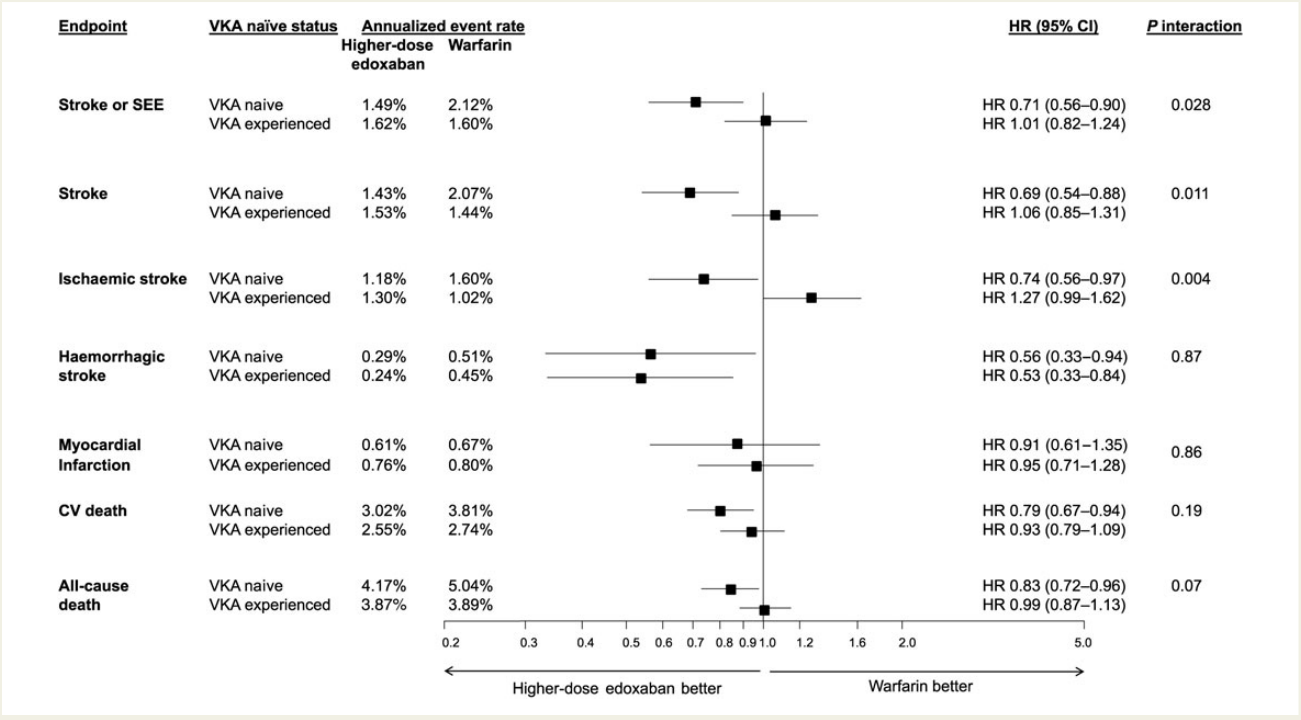

Figure 1 Efficacy of higher-dose edoxaban in the intention-to-treat population stratified by prior vitamin K antagonist exposure (vitamin K antagonist naive defined as ≤60 consecutive days of prior vitamin K antagonist use). *P* interaction reflects the two-way interaction between treatment arm and prior vitamin K antagonist exposure.

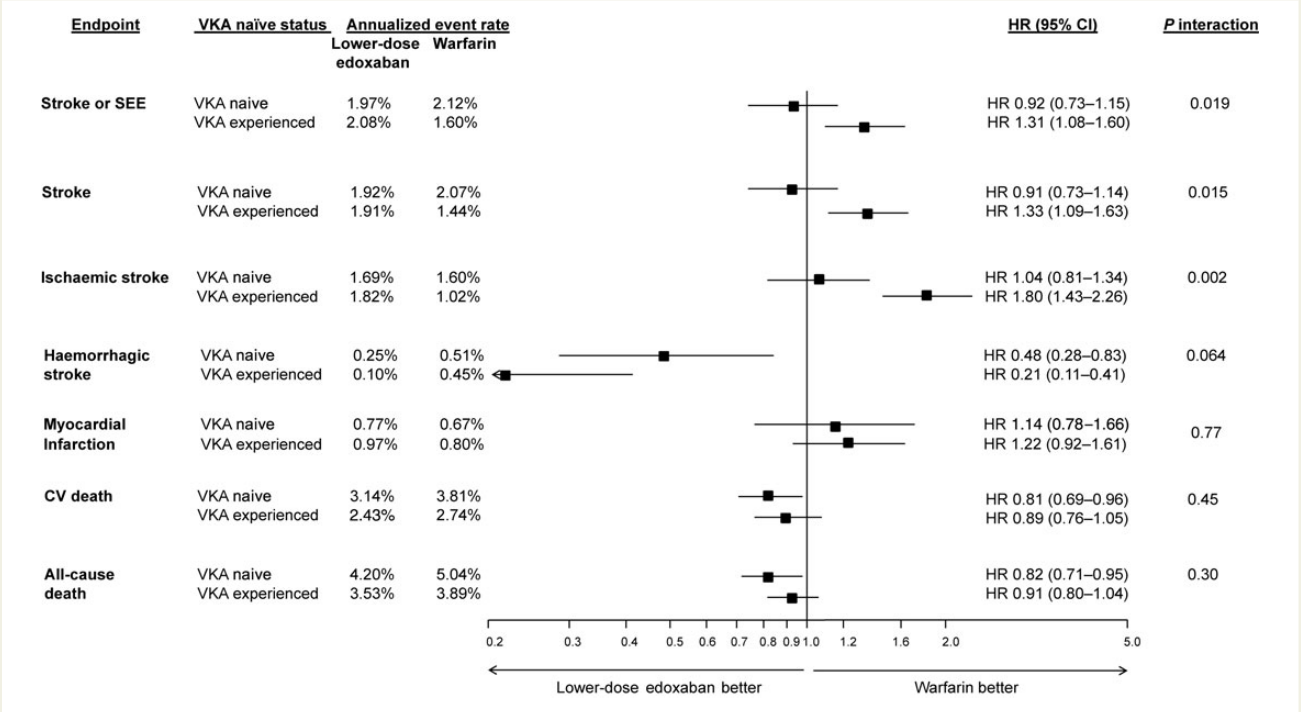

Figure 2 Efficacy of lower-dose edoxaban in the intention-to-treat population stratified by prior vitamin K antagonist exposure (vitamin K antagonist naive defined as ≤60 consecutive days of prior vitamin K antagonist use). *P* interaction reflects the two-way interaction between treatment arm and prior vitamin K antagonist exposure.

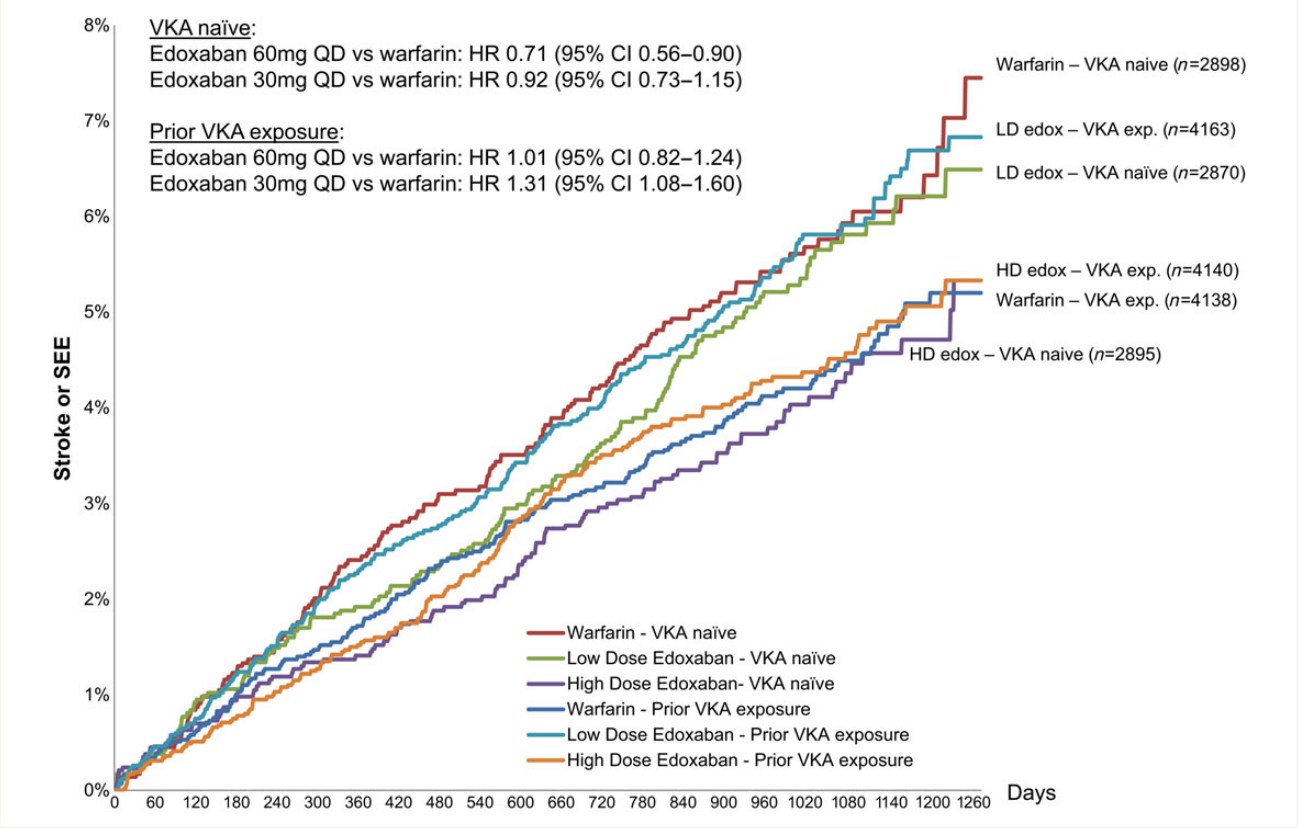

Figure 3 The cumulative incidence of stroke or systemic embolic event by treatment arm for those individuals who were vitamin K antagonist naive and those who were vitamin K antagonist experienced. A significant treatment interaction for edoxaban was observed based on prior vitamin K antagonist exposure [*P* for interaction (higher dose) = 0.028; *P* for interaction (lower dose) = 0.019].

Table 2 **Safety of edoxaban stratified by prior vitamin K antagonist exposure in the safety population**

Outcome	VKA naive	Warfarin	Higher-dose edoxaban			Lower-dose edoxaban		
		Event rate/ year (%)	Event rate/ year (%)	HR (95% CI) vs. warfarin	*P* interaction	Event rate/ year (%)	HR (95% CI) vs. warfarin	*P* interaction
Major bleed	Yes	3.64	2.88	0.80 (0.65–0.97)	0.90	1.80	0.49 (0.40–0.62)	0.71
	No	3.54	2.85	0.81 (0.69–0.95)		1.84	0.52 (0.43–0.63)	
Major or minor bleed	Yes	7.68	6.04	0.79 (0.69–0.91)	0.28	4.78	0.63 (0.54–0.73)	0.60
	No	8.60	7.49	0.87 (0.79–0.97)		5.62	0.66 (0.59–0.74)	
Fatal bleed	Yes	0.45	0.24	0.53 (0.28–1.00)	0.92	0.20	0.44 (0.23–0.85)	0.30
	No	0.32	0.18	0.56 (0.31–1.01)		0.08	0.26 (0.12–0.56)	
Life-threatening bleed	Yes	0.78	0.41	0.53 (0.33–0.85)	0.97	0.25	0.32 (0.18–0.56)	0.89
	No	0.81	0.43	0.54 (0.37–0.78)		0.27	0.33 (0.21–0.52)	
Intracranial haemorrhage	Yes	0.83	0.46	0.56 (0.35–0.88)	0.32	0.31	0.37 (0.22–0.62)	0.34
	No	0.82	0.33	0.41 (0.27–0.61)		0.21	0.26 (0.16–0.42)	

P interaction reflects the two-way interaction between treatment arm and prior VKA exposure.

Sensitivity analysis

As a sensitivity analysis, subjects were also stratified on the basis of whether or not they were taking a VKA at the time of randomization and whether or not they had any prior history of VKA exposure regardless of duration. The results were qualitatively consistent with those from the primary analysis (Supplementary material online, *Tables S1–S6*). A sensitivity analysis was also conducted that was restricted to the modified intention-to-treat population while

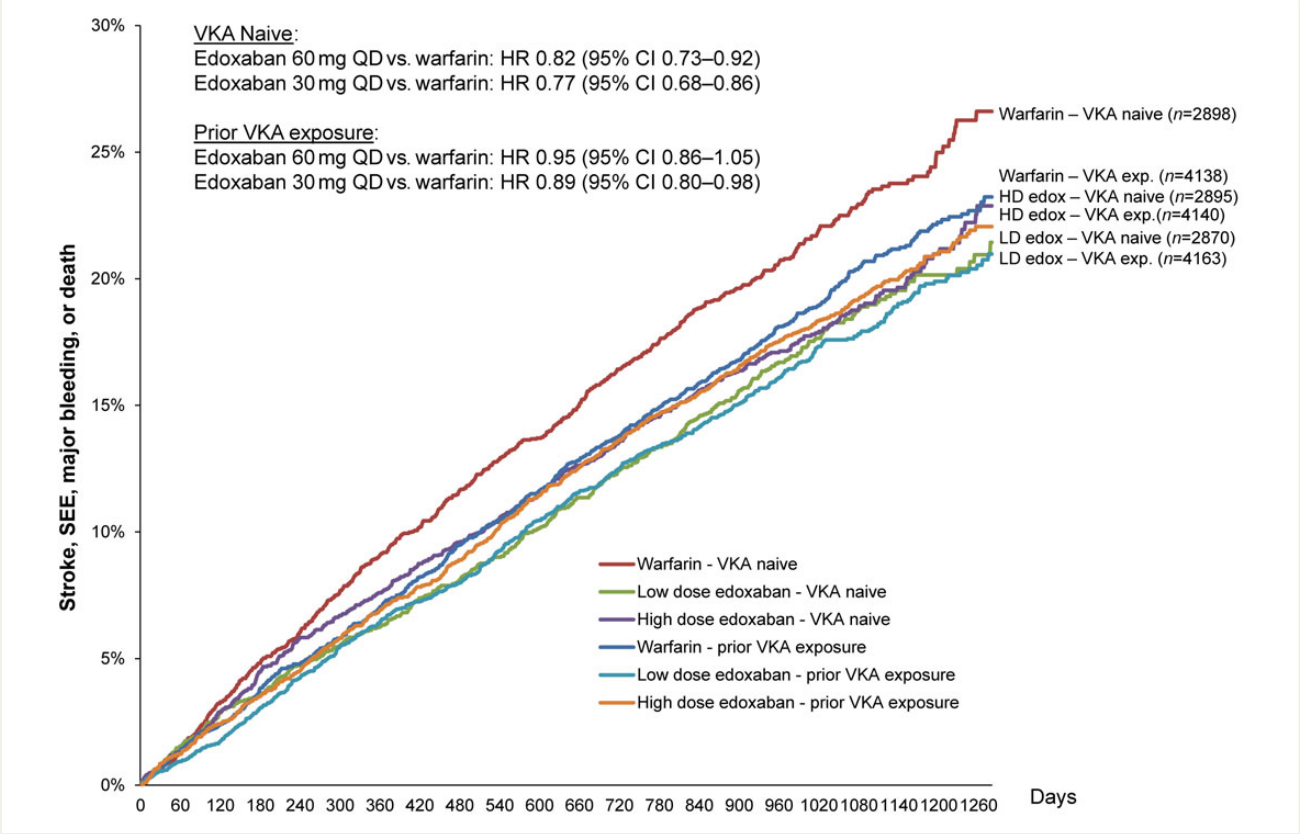

Figure 4 The cumulative incidence of the net clinical outcome of stroke, systemic embolic event, major bleeding, or death by treatment arm for those individuals who were vitamin K antagonist naive and those who were vitamin K antagonist experienced [*P* for interaction (higher dose) = 0.049; *P* for interaction (lower dose) = 0.055].

Table 3 The composite and net clinical outcomes for edoxaban vs. warfarin by prior vitamin K antagonist exposure

Outcome	VKA naive	Warfarin	Higher-dose edoxaban			Lower-dose edoxaban		
		Event rate/ year (%)	Event rate/ year (%)	HR (95% CI) vs. warfarin	*P* interaction	Event rate/ year (%)	HR (95% CI) vs. warfarin	*P* interaction
CV death, stroke, or SEE	Yes	5.30	4.05	0.77 (0.66–0.89)	0.029	4.49	0.83 (0.72–0.97)	0.018
	No	3.86	3.71	0.96 (0.84–1.10)		4.06	1.06 (0.93–1.21)	
All-cause death, stroke, or SEE	Yes	6.47	5.12	0.79 (0.69–0.91)	0.015	5.50	0.84 (0.73–0.96)	0.028
	No	4.98	4.94	0.99 (0.88–1.11)		5.05	1.02 (0.91–1.15)	
MACE[a]	Yes	5.80	4.49	0.78 (0.67–0.89)	0.016	5.11	0.87 (0.76–1.00)	0.022
	No	4.44	4.36	0.98 (0.86–1.11)		4.75	1.08 (0.95–1.22)	
Net clinical outcome 1[b]	Yes	8.88	7.25	0.82 (0.73–0.92)	0.049	6.88	0.77 (0.68–0.86)	0.055
	No	7.60	7.26	0.95 (0.86–1.05)		6.73	0.89 (0.80–0.98)	
Net clinical outcome 2[b]	Yes	6.05	4.80	0.79 (0.69–0.91)	0.036	4.79	0.78 (0.68–0.89)	0.19
	No	4.69	4.54	0.96 (0.85–1.09)		4.12	0.88 (0.78–1.00)	
Net clinical outcome 3[b]	Yes	6.89	5.36	0.78 (0.68–0.89)	0.017	5.59	0.80 (0.70–0.91)	0.029
	No	5.45	5.26	0.96 (0.86–1.08)		5.23	0.97 (0.86–1.08)	

P interaction reflects the two-way interaction between treatment arm and prior VKA exposure.
[a]MACE (major adverse cardiovascular event) includes the composite of death due to cardiovascular cause or bleed, myocardial infarction, stroke, or SEE.
[b]The primary net clinical outcome was a composite of stroke, systemic embolic event, major bleeding, or death from any cause. The secondary net clinical outcome was a composite of disabling stroke, life-threatening bleeding, or death from any cause. The tertiary net clinical outcome was a composite of stroke, systemic embolic event, life-threatening bleeding, or death from any cause.

on-treatment (Supplementary material online, *Tables S7* and *S8*), as well as on the basis of whether patients did or did not meet criteria for edoxaban dose reduction (Supplementary material online, *Tables S9* and *S10*). Directionally consistent results were observed for both sensitivity analyses based on prior VKA exposure, although fewer tests for interaction remained significant, this is perhaps explained by fewer total events while on-treatment and in the smaller dose-reduced groups.

Discussion

In patients with AF, edoxaban appeared to demonstrate greater efficacy when compared with warfarin in those patients who were VKA naive vs. those who were VKA experienced. Regardless of prior VKA exposure, higher-dose and lower-dose edoxaban significantly reduced the risk of major bleeding and intracranial haemorrhage when compared with warfarin.

Several factors have contributed to the rapid uptake in the use of NOACs in VKA naive and VKA experienced individuals, including their ease of administration, the lack of need for routine blood monitoring and fewer drug or food interactions. In the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial of dabigatran in patients with AF, randomization was stratified on the basis of prior VKA exposure ($\leq$62 days of prior lifetime VKA exposure and representing 50.4% of the study population), and the efficacy of dabigatran for stroke or SEE prevention was consistent in those who were VKA naive and those who were VKA experienced.[7] Similarly, the efficacy of apixaban was not modified by prior VKA exposure in the ARISTOTLE trial (Apixaban for Reduction in Stroke and Other Thromboembolic) despite a fairly marked difference in median percentage TTR between VKA naive and VKA experienced subjects (61.4 vs. 69.1%).[8] In the ROCKET-AF trial (Rivaroxaban Once-Daily, Oral, Direct, Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), a trend was observed towards a greater relative benefit towards stroke or SEE reduction with rivaroxaban in VKA naive subjects (HR 0.81, 95% CI 0.64–1.03 vs. HR 0.94, 95% CI 0.75–1.18); however, this difference between groups was not statistically significant (P interaction = 0.36).[9]

In the current analysis of 21 105 subjects with moderate-to-high risk AF, both higher-dose and lower-dose edoxaban appeared to demonstrate greater efficacy in individuals who were VKA naive, as compared with those with prior VKA exposure. Specifically, the higher-dose edoxaban regimen significantly reduced the risk of stroke or SEE when compared with warfarin in patients who were VKA naive, whereas the higher-dose edoxaban regimen had similar efficacy to warfarin in patients who were VKA experienced. A lower-dose edoxaban regimen was comparable with warfarin for stroke or SEE in patients who were VKA naive, but was associated with an increased risk of stroke or SEE in those who were VKA experienced. Regardless of prior VKA exposure, both higher-dose and lower-dose edoxaban significantly reduced the risk of major bleeding and intracranial haemorrhage.

The greater efficacy that was observed with edoxaban for thrombo-embolic event prevention in VKA naive patients appeared to be explained primarily by an increased incidence of ischaemic stroke in VKA naive patients who were treated with warfarin and/or a lower incidence of ischaemic stroke in VKA experienced subjects who were warfarin treated. In particular, the incidence of ischaemic stroke was 57% higher in VKA naive subjects treated with warfarin as compared with those who were VKA experienced, despite the fact that VKA experienced subjects had more cardiovascular risk factors and a higher average $CHADS_2$ score. In contrast, VKA naive patients treated with edoxaban tended to have a lower incidence of ischaemic stroke than those who were VKA experienced (11.8% lower across pooled edoxaban groups), as might have been predicted by their risk profile. These findings could suggest that edoxaban has a consistent biological effect regardless of prior VKA exposure, but that there exists a higher risk of stroke or embolic events in VKA naive patients or a lower risk in VKA experienced subjects treated with warfarin. Nonetheless, we cannot exclude the possibility that any baseline characteristics or comorbidities that were imbalanced between VKA naive and VKA experienced patients may also have modified the efficacy or safety profile of edoxaban. Notably, the differential benefit of edoxaban that was observed in VKA naive vs. VKA experienced patients appeared to persist over time, therefore characteristics that differed between the two groups may have contributed to the higher median TTR in VKA experienced patients throughout follow-up. Further, median TTR remains a relatively crude metric since it is centre-based and does not account for the inter-patient variability that might be observed at an individual site. Since it appears that the current treatment interaction was explained by a differential response to warfarin, rather than the biological effects of edoxaban, these findings do not suggest that the choice of NOAC should be influenced by prior VKA experience. However, since the observed median TTR was higher in the ENGAGE AF-TIMI 48 trials than other contemporary trials of NOAC therapy in patients with AF, it raises for consideration whether a patient who has been very well controlled on VKA therapy will derive as much benefit for ischaemic stroke protection when they transition to NOAC therapy as a patient who is VKA naive.

The current observations from the ENGAGE AF-TIMI 48 trial are consistent with those from the ACTIVE-W (Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events) trial that compared warfarin to aspirin and clopidogrel for stroke prevention and found that the benefit of VKA therapy for reducing thrombo-embolic events was more pronounced in those who were on a VKA at study entry.[10] Further, in ACTIVE-W, the observed benefit with warfarin over antiplatelet therapy was only apparent in patients who were enrolled at centres with a percentage TTR above the median.[11] A similar trend towards a greater treatment benefit with warfarin therapy was observed for those who were VKA experienced in the BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged Study) trial that compared warfarin to aspirin, although the interaction did not achieve significance.[12] These observations from prior studies are perhaps not surprising since prior VKA exposure, in addition to a higher median percentage TTR, has been previously demonstrated to be associated with a decreased risk of stroke in warfarin-treated patients.[4,13] To that end, patients with prior VKA exposure have had the opportunity to demonstrate that they are warfarin 'tolerant' unlike those who are VKA naive. Since the four recent trials of NOAC therapy differed subtly in terms of definitions for VKA exposure, the proportion and characteristics of those who were VKA naive, the median percentage TTR with warfarin and rates

of study-drug discontinuation, these variables may have been sufficient to attenuate a potential treatment interaction.

Limitations to the current analysis warrant consideration. Although the current subgroup analysis was pre-specified, we cannot exclude the possibility that the observed treatment interaction can be explained by chance. Although the test for interaction was attenuated in the on-treatment study population, the test was inadequately powered to detect a difference between subgroups. As well, there were baseline differences that existed between subjects who were VKA naive vs. VKA experienced; therefore, some of these other characteristics may have formed the basis of the observed interaction. Of note, aspirin use was more frequent at baseline and throughout follow-up in patients who were VKA naive as compared with those who were VKA experienced. However, since both edoxaban and warfarin-treated patients in the VKA naive group were more likely to receive aspirin, one might anticipate that this would partly attenuate, rather than exaggerate, the apparent efficacy for edoxaban in the VKA naive group relative to those who were VKA experienced. Of interest, it is notable that VKA naive patients who were warfarin treated had a relatively higher risk of thrombo-embolic events despite a lower average $CHADS_2$ score than those warfarin-treated patients who were VKA experienced. This observation supports previous reports that prior VKA use may be a relevant predictor of future embolic risk.[4]

In conclusion, the current findings suggest greater efficacy with edoxaban compared with warfarin for stroke or SEE prevention in VKA naive subjects than in those who are VKA experienced. These observations appear to be explained by a higher risk of ischaemic stroke in VKA naive patients who are warfarin treated and/or a lower incidence of ischaemic stroke in those who are VKA experienced. These findings contribute to a greater understanding of efficacy and safety of in the growing population of patients who are VKA naive or experienced and initiating NOAC therapy.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Funding

The ENGAGE AF-TIMI 48 trial was funded by Daiichi Sankyo Pharma Development. The current analysis did not receive any additional funding.

Conflict of interest: M.L.O. has received grants from Merck, AstraZeneca, GlaxoSmithKline, and Eisai. R.P.G. reports receiving consulting fees from Daiichi Sankyo, Janssen Pharmaceuticals, and Merck; lecture fees from Bristol-Myers Squibb, Daiichi Sankyo, Merck, and Sanofi; and grant support through his institution from Daiichi Sankyo, Merck, Johnson & Johnson, Sanofi, and AstraZeneca. C.T.R. reports receiving consulting fees from Daiichi Sankyo, Bristol-Myers Squibb, and Boehringer Ingelheim and grant support through his institution from Daiichi Sankyo. E.B. reports receiving consulting fees from Sanofi, Genzyme, Amorcyte, the Medicines Company, and Cardiorentis; lecture fees from Eli Lilly, Menarini, Medscape, and Bayer HealthCare; and grant support through his institution from Daiichi Sankyo, AstraZeneca, Johnson & Johnson, GlaxoSmithKline, Bristol-Myers Squibb, Beckman Coulter, Roche Diagnostics, Pfizer, Merck, and Sanofi. He also reports serving as an unpaid consultant for Merck and providing uncompensated lectures for Merck and CVRx. M.S., H.R., and M.M. report being employees of Daiichi Sankyo. M.M. also reports holding a pending patent related to the clinical properties of edoxaban. S.A.M. and E.M.A. report receiving grant support through their institution from Daiichi Sankyo.

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