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Edoxaban vs. warfarin in patients with atrial fibrillation on amiodarone: a subgroup analysis of the ENGAGE AF-TIMI 48 trial

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Background In the ENGAGE AF-TIMI 48 trial, the higher-dose edoxaban (HDE) regimen had a similar incidence of ischaemic stroke compared with warfarin, whereas a higher incidence was observed with the lower-dose regimen (LDE). Amiodarone increases edoxaban plasma levels via P-glycoprotein inhibition. The current pre-specified exploratory analysis was performed to determine the effect of amiodarone on the relative efficacy and safety profile of edoxaban.

Methods and results At randomization, 2492 patients (11.8%) were receiving amiodarone. The primary efficacy endpoint of stroke or systemic embolic event was significantly lower with LDE compared with warfarin in amiodarone treated patients vs. patients not on amiodarone (hazard ratio [HR] 0.60, 95% confidence intervals [CIs] 0.36–0.99 and HR 1.20, 95% CI 1.03–1.40, respectively; *P* interaction <0.01). In patients randomized to HDE, no such interaction for efficacy was observed (HR 0.73, 95% CI 0.46–1.17 vs. HR 0.89, 95% CI 0.75–1.05, *P* interaction = 0.446). Major bleeding was similar in patients on LDE (HR 0.35, 95% CI 0.21–0.59 vs. HR 0.53, 95% CI 0.46–0.61, *P* interaction = 0.131) and HDE (HR 0.94, 95% CI 0.65–1.38 vs. HR 0.79, 95% CI 0.69–0.90, *P* interaction = 0.392) when compared with warfarin, independent of amiodarone use.

Conclusions Patients randomized to the LDE treated with amiodarone at the time of randomization demonstrated a significant reduction in ischaemic events vs. warfarin when compared with those not on amiodarone, while preserving a favourable bleeding profile. In contrast, amiodarone had no effect on the relative efficacy and safety of HDE.

Keywords Edoxaban • Anticoagulation • Amiodarone • Atrial fibrillation

Introduction

In the effective anti-coagulation with factor Xa next generation in atrial fibrillation (AF)–thrombolysis in myocardial infarction 48 (ENGAGE AF-TIMI 48) trial, two dosing regimens of the direct factor Xa inhibitor edoxaban were found to be non-inferior to well-managed warfarin for the prevention of stroke or systemic embolic events (SEEs) in patients with AF.[1] In addition, both regimens of edoxaban significantly reduced the risk of major bleeding and cardiovascular death when compared with warfarin. The lower-dose (LD) regimen of edoxaban, however, was associated with a 41% relative increase in ischaemic stroke when compared with warfarin.

Edoxaban acts as a substrate for the efflux transporter p-glycoprotein (P-gp), located primarily in the intestine, which limits systemic absorption of drugs by pumping them back into the intestinal lumen.[2–4] Edoxaban underwent extensive preclinical testing to determine the optimal dosing for patients co-treated with P-gp inhibitors. Co-administration of edoxaban with strong P-gp inhibitors verapamil, quinidine, and dronedarone significantly increased maximal edoxaban drug levels (C_{max}), the area under the curve, and trough (C_{min}) plasma levels.[5] Based on these findings, as well as on further modelling and simulation of edoxaban exposure and response relationships,[5] a 50% dose reduction was implemented in the ENGAGE AF-TIMI 48 trial for patients taking these drugs. In contrast, amiodarone is a weaker P-gp inhibitor; based on drug–drug

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interaction studies there was no dose reduction implemented in the ENGAGE AF-TIMI 48 trial for concomitant amiodarone use.

Amiodarone is one of the most frequently used anti-arrhythmic drugs in patients with AF, in spite of its pronounced side effect profile as well as numerous drug–drug interactions.[6] Amiodarone decreases hepatic metabolism of warfarin by inhibiting cytochrome P450-dependent elimination pathways, necessitating frequent dose adjustments to counterbalance its potentiating effect on the degree of anti-coagulation. In view of its widespread use, potential interactions with non-vitamin K oral anti-coagulants (NOACs) such as edoxaban are of great clinical importance for a large number of patients. In the current pre-specified exploratory analysis, we evaluated the efficacy and safety of edoxaban in patients co-treated with amiodarone in the ENGAGE AF-TIMI 48 trial.[1] Since a prior analysis of edoxaban concentration in this trial demonstrated correlations with clinical efficacy and safety,[7] we also explored the impact of concomitant amiodarone use on edoxaban concentration and outcomes.

Methods

Study population and procedures

The design and main results of the phase 3 multinational, double-blind, double-dummy, non-inferiority ENGAGE AF-TIMI 48 trial have previously been reported.[1,2] In brief, 21′105 patients with AF at moderate-to-high risk of stroke were randomized to receive higher-dose (HD) edoxaban (60 mg once daily), LD edoxaban (30 mg once daily), or warfarin. In patients with an estimated creatinine clearance 30–50 mL/min, body weight ≤60 kg, or in those requiring concomitant use of verapamil, quinidine, or dronedarone, the edoxaban dose was reduced by 50% (HD edoxaban: 60–>30 mg; LD edoxaban 30 mg–>15 mg). The ENGAGE AF-TIMI 48 trial was unique among the trials comparing NOACs vs. warfarin in that dose reductions were performed not only at randomization but also throughout the trial if a patient subsequently met a criteria requiring dose reductions. Patients were eligible for inclusion in ENGAGE AF-TIMI 48 if they were 21 years of age or older, had AF documented within the 12 months prior to randomization, a $CHADS_2$ score ≥2, and anti-coagulation therapy planned for the duration of the trial.[1] Most important exclusion criteria were AF due to a reversible cause, severe renal insufficiency (creatinine clearance <30 mL per minute), a high risk of bleeding, use of dual anti-platelet therapy, and moderate-to-severe mitral stenosis.[2] Mean follow-up of the study was 2.8 years, which was the longest of all major NOAC trials.

Endpoints

Efficacy outcomes analysed included stroke or SEEs (the primary efficacy endpoint), ischaemic stroke, haemorrhagic stroke, all-cause and cardiovascular mortality.[1] Safety outcomes included International Society on Thrombosis and Haemostasis[8] major bleeding (principal safety endpoint), clinically relevant non-major bleeding, and intracranial haemorrhage.[2] An independent clinical events committee blinded to randomized treatment assignment adjudicated all events.

Statistical analysis

In the ENGAGE AF-TIM 48 study, the only randomization stratification variables were $CHADS_2$ score and dose adjustment.[1] For the current analysis, the relative effect of edoxaban vs. warfarin in patients on amiodarone at trial entry was compared the relative effect of edoxaban vs. warfarin in patients *not* on amiodarone. Hazard ratios (HRs) for edoxaban and warfarin with 95% confidence intervals (CIs) stratified by amiodarone use at trial entry were calculated with the Cox proportional hazards models (along with the randomization stratification factors of $CHADS_2$ score and dose adjustment status). We performed in addition a multivariable sensitivity analysis to account for differences in baseline characteristics across randomized treatment groups in patients taking amiodarone as outlined in *Table 1* (age ≥75 years, heart failure, and hypertension).

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. Event rates were expressed per 100 patient-years. Efficacy analyses were analysed in the intention-to-treat study population and bleeding outcomes in the safety population which included all patients who had received at least one dose of study drug. All tests were two sided with a *P*-value <0.05 considered to be significant. The TIMI Study Group has an independent copy of the trial database and conducted all analyses. Analyses were performed with use of Stata/SE version 12.1 (Stata Corp., College Station, TX, USA).

Results

Baseline characteristics

At randomization, 2492 patients (11.8%) were receiving amiodarone. Patients receiving amiodarone at baseline were equally distributed among the three treatment arms (*Table 1*). As expected for a large randomized clinical trial, baseline characteristics among patients on amiodarone were very similar among the three treatment arms. Patients on amiodarone at randomization who were assigned to warfarin were more likely to be ≥75 years of age, but less likely to have prior CHF or hypertension than patients assigned to edoxaban. There were no significant differences between the three treatment arms in patients without amiodarone at baseline (Supplementary material online, *Table S1*).

Over the entire study cohort, patients on amiodarone at randomization were younger and overall had fewer comorbidities than patients not receiving the drug, except for a higher prevalence of coronary artery disease and congestive heart failure (Supplementary material online, *Table S2*). Of note, patients on amiodarone were less frequently in the INR target range when compared with those not on the drug (% time in therapeutic range [INR 2.0–3.0]: 64.0% [interquartile range, 52.4–73.2%] vs. 69.0% [interquartile range, 57.1–77.9%], $P < 0.001$), likely secondary to drug–drug interaction between amiodarone and warfarin.

Efficacy of edoxaban vs. warfarin in amiodarone-treated patients

A significant interaction for amiodarone use vs. non-use was observed for several efficacy endpoints in patients randomized to LD edoxaban vs. warfarin (*Figure. 1*). There was significantly greater relative efficacy with LD edoxaban compared with warfarin in patients on amiodarone at baseline compared with those not on amiodarone for the primary endpoint of stroke or SEE (HR 0.60, 95% CI 0.36–0.99 and HR 1.20, 95% CI 1.03–1.40 for amiodarone and no amiodarone patients, respectively; *P* interaction = 0.009), and the pre-specified net clinical endpoints of death, stroke, SEE, or

Table 1 Baseline characteristics per randomization group of patients treated with amiodarone at baseline

	Edo low dose (%) *N* = 799	Edo high dose (%) *N* = 866	Warfarin (%) *N* = 827	*P*-value
Age (years)	69 (61–76)	68 (61–75)	69 (61–76)	0.081
Age ≥75 years	242 (30.3%)	235 (27.1%)	274 (33.1%)	0.027
Male gender	469 (58.7%)	548 (63.3%)	508 (61.4%)	0.157
Region				0.523
North American	100 (12.5%)	128 (14.8%)	111 (13.4%)	
Latin American	173 (21.7%)	169 (19.5%)	178 (21.5%)	
Western Europe	97 (12.1%)	119 (13.7%)	89 (10.8%)	
Eastern Europe	333 (41.7%)	348 (40.2%)	338 (40.9%)	
Asia, Japan and South Africa	96 (12%)	102 (11.8%)	111 (13.4%)	
Type of afib				0.690
Paroxysmal	334 (41.8%)	338 (39%)	347 (42%)	
Persistent	211 (26.4%)	244 (28.2%)	213 (25.8%)	
Permanent	254 (31.8%)	284 (32.8%)	267 (32.3%)	
CHADS2 score (mean)	2.7 (0.9)	2.8 (0.9)	2.8 (0.9)	0.169
CHADS2 score >3	154 (19.3%)	177 (20.4%)	170 (20.6%)	0.776
CrCl at randomization (mL/min)	70.0 (52.1–93.0)	69.4 (52.9–91.5)	69.5 (52.0–89.9)	0.666
History of stroke or TIA	191 (23.9%)	208 (24%)	210 (25.4%)	0.736
History of CHF	543 (68%)	630 (72.7%)	552 (66.7%)	0.018
History of diabetes	234 (29.3%)	285 (32.9%)	278 (33.6%)	0.134
History of hypertension	768 (96.1%)	837 (96.7%)	780 (94.3%)	0.047
Prior MI	110 (13.8%)	113 (13%)	93 (11.3%)	0.292
VKA naive	432 (54.1%)	428 (49.4%)	416 (50.3%)	0.136
Dose reduced at randomization[a]	214 (26.8%)	218 (25.2%)	215 (26%)	0.755
Medication use at randomization				
Aspirin	256 (32%)	290 (33.5%)	275 (33.3%)	0.800
Thienopyridine	26 (3.3%)	21 (2.4%)	20 (2.4%)	0.487
Digoxin or digitalis preparations	160 (20%)	179 (20.7%)	166 (20.1%)	0.935

Data are presented as medians (interquartile ranges) for continuous variables and frequencies for categorical variables.
[a]In patients with an estimated creatinine clearance 30–50 mL/min, body weight ≤60 kg, or in those requiring concomitant use of verapamil, quinidine, or dronedarone, the edoxaban dose was reduced by 50% (HD edoxaban: 60→30 mg; LD edoxaban 30 mg→15 mg).

major bleed (*P* interaction = 0.016), and death, stroke, SEE, or life-threatening bleed (*P* interaction = 0.014). No significant interaction with respect to amiodarone use at baseline was observed for HD edoxaban.

As outlined above, baseline characteristics among patients on amiodarone were very similar among the three treatment arms. A sensitivity analysis was consistent after multivariable adjustment for differences in baseline characteristics across randomized treatment groups in patients taking amiodarone as outlined in *Table 1* (age ≥75 years, heart failure, and hypertension), with interaction *P*-values for stroke/SEE *P* = 0.012 for the LD group and *P* = 0.533 for the HD group. Indeed, two of these three variables in fact indicate a potentially higher risk for stroke in the edoxaban arms when compared with warfarin (higher percentage of patients with a history of heart failure, and of patients with a history of hypertension).

Safety of edoxaban vs. warfarin in amiodarone-treated patients

Lower-dose edoxaban and HD edoxaban significantly reduced major bleeding by 53 and 20%, respectively, compared with warfarin.[1] No significant interaction by baseline amiodarone use was observed in patients randomized to LD edoxaban for any bleeding outcome (*Figure. 2*). For HD edoxaban, there was no interaction by baseline amiodarone use for major bleeding but there was greater relative major plus clinically relevant non-major bleeding compared with warfarin in HD edoxaban patients on amiodarone at baseline (HR 1.12, 95% CI 0.91–1.36) vs. those who were not (HR 0.83, 95% CI 0.77–0.89; *P* interaction 0.008). There was no interaction by amiodarone use at baseline in HD edoxaban patients with respect to more severe bleeding outcomes such as intracranial haemorrhage, life-threatening bleeding, or fatal bleeding.

A sensitivity analysis was consistent after multivariable adjustment for differences in baseline characteristics across randomized treatment groups in patients taking amiodarone as outlined in *Table 1* (age ≥75 years, heart failure, and hypertension), with interaction *P*-values for major bleed *P* = 0.161 and *P* = 0.275 for the LD and HD group, respectively. Indeed, two of these three variables in fact indicate a potentially higher risk for bleeding in the edoxaban arms when compared with warfarin (higher percentage of patients with a history of heart failure, and of patients with a history of hypertension).

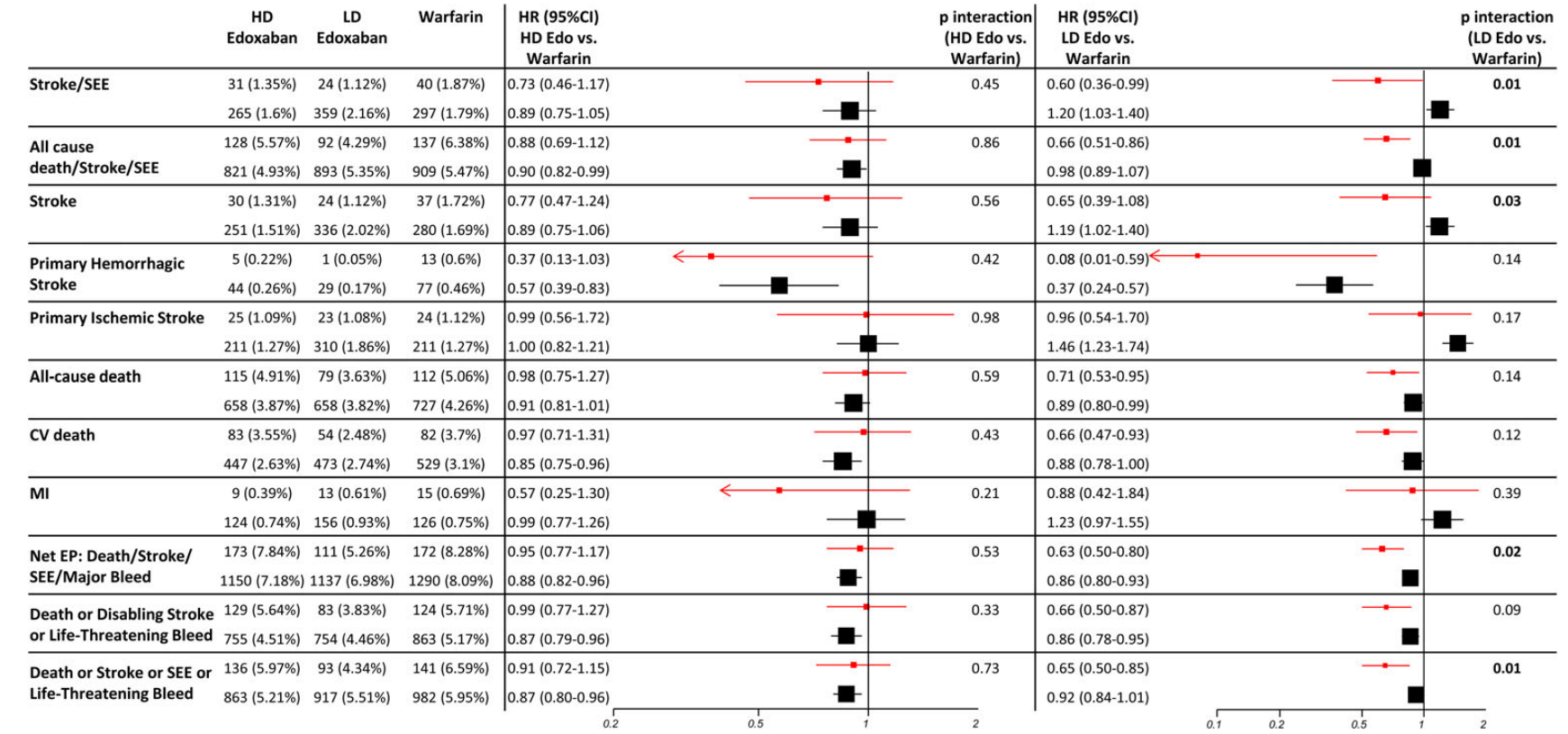

Figure 1 Efficacy of edoxaban vs. warfarin in patients with and without amiodarone at baseline. Number of evens and event rates (%/year), as well as hazard ratios for higher-dose and lower-dose edoxaban are shown for patients with (red, upper row) and without (black, lower row) amiodarone. A sensitivity analysis was consistent after multivariable adjustment for differences in baseline characteristics across randomized treatment groups in patients taking amiodarone as outlined in *Table 1* (age $\geq$75 years, heart failure, and hypertension): Interaction *P*-values for stroke/SEE $P = 0.012$ for the lower-dose group and $P = 0.533$ for the higher-dose group. CV, cardiovascular; EP, endpoint; MI, myocardial infarction; SEE, systemic symbolic event.

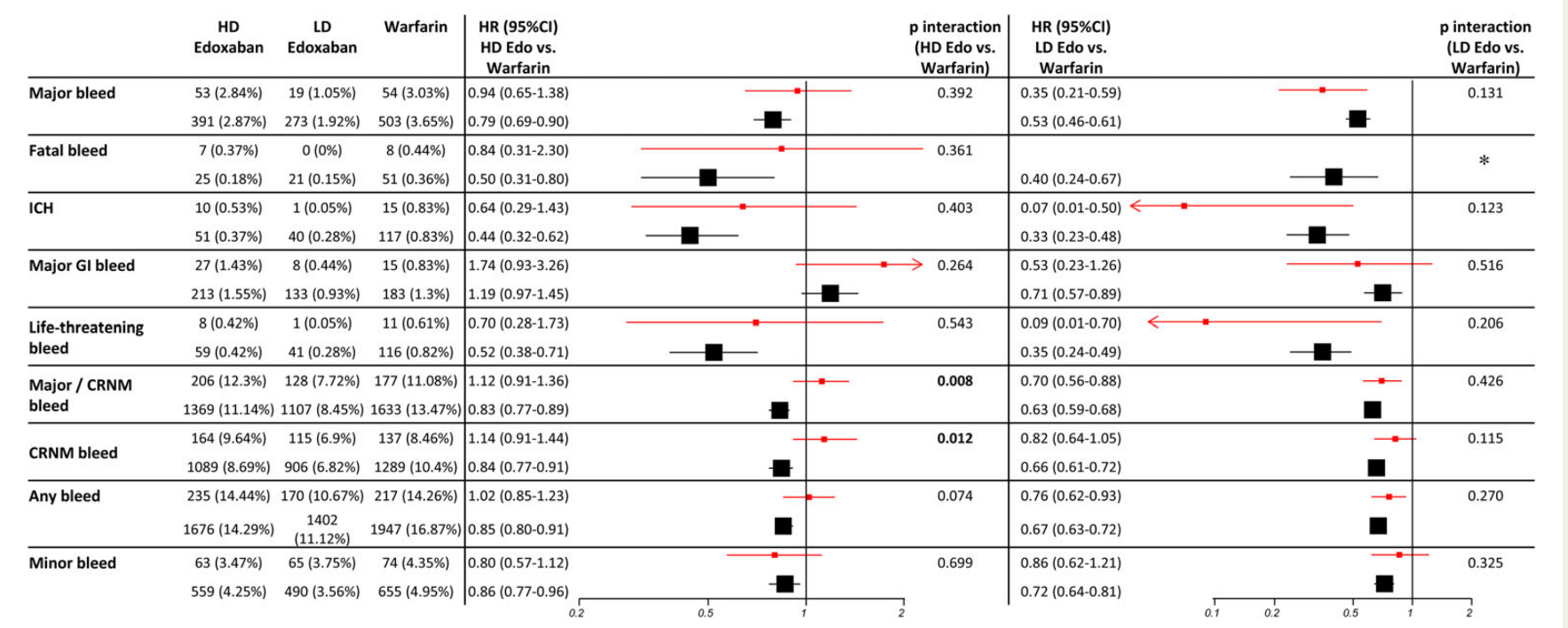

Figure 2 Safety of edoxaban vs. warfarin in patients with and without amiodarone at baseline. Number of evens and event rates (%/year), as well as hazard ratios for higher-dose and lower-dose edoxaban are shown for patients with (red, upper row) and without (black, lower row) amiodarone. A sensitivity analysis was consistent after multivariable adjustment for differences in baseline characteristics across randomized treatment groups in patients taking amiodarone as outlined in *Table 1* (age ≥75 years, heart failure, and hypertension): Interaction *P*-values for major bleed $P = 0.161$ and $P = 0.275$ for the lower-dose and higher-dose group, respectively. CRNM, clinically relevant non-major; GI, gastrointestinal; ICH, intracranial haemorrhage. * No interaction *P* calculated as $n = 0$ for patients on lower-dose edoxaban and amiodarone.

Edoxaban drug levels

Edoxaban trough concentrations at 1 month post-randomization were available in 6780 of the 14,069 patients randomized to edoxaban. In both edoxaban regimens, amiodarone was associated with significantly increased trough levels compared with patients not on amiodarone: LD edoxaban: with amiodarone 27.3 ng/mL ± 24.5 ng/mL vs. no amiodarone 21.9 ± 20.8 ng/mL, $P < 0.001$; HD edoxaban: with amiodarone 58.5 ± 53.2 ng/mL vs. no amiodarone 43.2 ± 41.1 ng/mL, $P < 0.001$.

Discussion

Amiodarone is among the most frequently prescribed and effective anti-arrhythmic drugs used in patients with AF.[6] Although amiodarone use is complicated by its side effect profile, it is one of the only anti-arrhythmics that can be used in the large proportion of patients with structural heart disease, heart failure, and coronary artery disease (in contrast to other anti-arrhythmics such as class Ic agents or dronedarone, which are contraindicated in these patients). Furthermore, only a negligible proportion of amiodarone is cleared via the kidneys, making it an attractive treatment option in patients with renal impairment, whereas dose adjustment is necessary with other agents (e.g. propafenone and dofetilide). On the other hand, amiodarone is known to interact with VKA, leading to more difficult INR control, as demonstrated by our data.

In the current pre-specified subgroup analysis, patients randomized to LD edoxaban who were taking amiodarone at baseline had fewer ischaemic events compared with warfarin vs. patients not on amiodarone. Importantly, the improved efficacy of LD edoxaban in amiodarone treated patients did not result in an increase in bleeding across the full range of severity. In contrast, the efficacy of HD edoxaban compared with warfarin was similar in patients treated with and without amiodarone at baseline. Although an increase in clinically relevant non-major bleeds associated with concomitant amiodarone use in the HD edoxaban group was observed, there was no effect on major or life-threatening bleeds.

Differential relative efficacy and safety between high dose and low dose edoxaban in amiodarone-treated patients

The increase in the relative efficacy of LD edoxaban compared with warfarin in patients taking amiodarone is likely to be mediated by the increased edoxaban concentration that was observed due to inhibition of P-gp by amiodarone. Interestingly, although concomitant amiodarone also increased the concentration of HD edoxaban, there was no corresponding increase in efficacy compared with warfarin. Conversely, the increase in concentration in LD edoxaban patients taking amiodarone did not result in an excess in any type of bleeding compared with warfarin, while a similar increase in concentration in HD edoxaban patients resulted in an increase in clinically relevant non-major bleeding (although not major or more serious types of bleeding). What explains the differential efficacy and safety between HD and LD edoxaban in amiodarone-treated patients? In a previous analysis from ENGAGE AF-TIMI 48, we observed that increased edoxaban concentration is inversely associated with the risk of stroke or systemic embolism; the slope of the association, however, was modest. In contrast, a much steeper association was observed for major bleeding.[7] Our current observations are in line with this analysis. Increase in plasma levels caused by co-administration of amiodarone in LD edoxaban patients occurs at an inflection point in the dose–response curve for efficacy, resulting in a significant reduction in ischaemic events. At the same time, this increase in concentration still falls within the 'flatter' part of the dose–response curve for bleeding. In contrast, the increase in concentration in HD edoxaban patients taking amiodarone occurs during the 'flat' portion of the dose–response curve for efficacy, resulting in no further increase in the reduction of ischemic events. The increased concentration for HD edoxaban does fall, however, on the steeper part of the dose–response curve for bleeding.

Amiodarone co-treatment with other non-vitamin K oral anti-coagulants

The oral direct thrombin inhibitor dabigatran, as well as the oral factor Xa inhibitors rivaroxaban and apixaban have all demonstrated non-inferior or superior efficacy for stroke prevention in AF when compared with warfarin.[9–12] Dabigatran, rivaroxaban, and apixaban all undergo P-gp-dependent metabolism, to varying degrees. Amiodarone leads to plasma level increases in pharmacokinetic trials of 12–60% for dabigatran.[13,14] Furthermore, amiodarone and its metabolite are inhibitors of Cytochrome P450 (CYP 450) 3A4. While rivaroxaban and apixaban are both metabolized by ~32% by CYP 450 3A4, it is only marginally involved (<4%) in the metabolism of edoxaban and dabigatran.[15]

As outlined above, we studied two dose regimens of edoxaban and our findings suggest that the dose–response curve is not linear with respect to prevention of stroke/SEE. A modest increase in edoxaban drug levels in patients receiving amiodarone in the HD edoxaban group did not appear to confer greater efficacy, likely because a change at this end of the dose–concentration curve is not that important regarding efficacy. In contrast, the increase in edoxaban concentration in patients receiving amiodarone did confer greater treatment effect, suggesting a steeper relationship between drug concentration and protection from stroke/SEE at the lower range of edoxaban concentrations. We note that there was a similar directional trend with low dose dabigatran 110 mg BID in RE-LY, but not with the HD dabigatran.[10,16] Our findings in ENGAGE AF-TIMI 48 may have been even more apparent since the two dose regimens of edoxaban differed by a factor of 2.0, where in RE-LY the two doses differed by a factor of 1.36. Finally, there was only one dose regimen studied with rivaroxaban and apixaban in ROCKET-AF and ARISTOTLE, respectively. We speculate that these dose regimens are at the higher end of the dose response (i.e. more similar to edoxaban HD and dabigatran 150 BID) where a modest increase in FXa inhibition due to amiodarone may not translate in an apparent clinical benefit.

Limitations

Although pre-specified, this subgroup analysis of the ENGAGE AF-TIMI 48 should be interpreted as hypothesis generating. While baseline parameters only differed slightly in three variables (percentage of patients >75 years, history of CHF, and history of hypertension), therapy with amiodarone was not randomized nor stratified

leaving the possibility of unmeasured residual confounding and bias through multiple testing. Although a biologically plausible explanation of our study's findings can be deducted from previous analyses from ENGAGE AF-TIMI 48, a chance finding cannot be ruled out due to multiple testing and the sample size of the subgroup (2492 patients, 11.8% of total study population). We used conventional significance levels for testing interactions with large enough differences observed in the magnitudes of the HRs for the primary efficacy endpoint between the two groups. As always, results of subgroup analyses need to be interpreted with caution in the context of power and type I error. Furthermore, our analysis was limited to amiodarone use at randomization and did not account for the amiodarone potentially being discontinued or initiated during the course of the trial. However, analyzing and censoring outcome events upon discontinuation of amiodarone would be subject to substantial flaws, including loss of randomization by using a post-randomization variable as well as the inherent difficulty to predict any residual effect of amiodarone at the time of a subsequent event in view of its long half-life (mean 60 days).

Conclusions

Patients randomized to the LD edoxaban regimen treated with amiodarone at the time of randomization demonstrated a significant reduction in ischaemic events vs. warfarin when compared with those not on amiodarone, while preserving a favourable bleeding profile. In contrast, no additional efficacy was observed in amiodarone-treated patients randomized to HD edoxaban at a cost of more clinically relevant non-major bleeding. These results indicate that in patients of ENGAGE AF-TIMI 48 co-administered with amiodarone, LD edoxaban achieves a 'sweet spot' between protection from ischaemic events and bleeding.

Supplementary material

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

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Conflict of interest: J.S, reports receiving received consulting and lecture fees from Amgen, Astra-Zeneca, Bayer, Biotronik, Biosense Webster, Boehringer-Ingelheim, Boston Scientific, Bristol-Myers Squibb, Daiichi-Sankyo, Cook Medical, Medtronic, Pfizer, Sanofi-Aventis, Sorin, and St. Jude Medical. He also reports grant support through his institution from Bayer and Daiichi-Sankyo. He is co-director of CorXL. R.P.G. reports receiving consulting fees from Bristol-Myers Squibb, Janssen, Daiichi-Sankyo, Merck, Pfizer, Portola, and Sanofi; and grant support to his institution from Daiichi-Sankyo, Merck, Johnson & Johnson, Sanofi, and Astra-Zeneca. E.B. reports receiving consulting fees from The Medicines Company, lecture fees from Menarini and Medscape, and grant support through his institution from Daiichi Sankyo, Astra-Zeneca, Merck & Co., and GlaxoSmithKline. He also reports serving as an unpaid consultant for Merck and Novartis, and providing uncompensated lectures for Merck & Co. Ms Murphy reports receiving grant support through her institution from Daiichi Sankyo. D.A. reports receiving consulting and lecture fees from Amgen, Astra-Zeneca, Bayer Healthcare, Boehringer-Ingelheim, Bristol-Myers Squibb, Cardiome, MSD, Novartis, Pfizer, Roche-Diagnostics, Sanofi-Aventis, and Vifor Pharma. H.H. reports receiving consulting fees as member of the scientific advisory boards and lecture feed from Boehringer-Ingelheim, Bayer, BMS-Pfizer, Daiichi-Sankyo, Merck, and Sanofi-Aventis. A.J.C. reports receiving received consulting and lecture fees from Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, and Pfizer. He also reports grant support through his institution from Bayer, Bristol-Myers Squibb, Daiichi-Sankyo, and Pfizer. E.M.A. reports receiving grant support through his institution from Daiichi Sankyo. C.T.R. reports receiving consulting fees from Bayer, Daiichi Sankyo, Portola, and Boehringer-Ingelheim and grant support through his institution from Daiichi Sankyo, Astra-Zeneca, Eisai, and Intarcia.

References

1. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Spinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM, the EAFTI. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;**369**:2093–2104.
2. Ruff CT, Giugliano RP, Antman EM, Crugnale SE, Bocanegra T, Mercuri M, Hanyok J, Patel I, Shi M, Salazar D, McCabe CH, Braunwald E. Evaluation of the novel factor xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: Design and rationale for the effective anticoagulation with factor xa next generation in atrial fibrillation-thrombolysis in myocardial infarction study 48 (engage af-timi 48). *Am Heart J* 2010;**160**:635–641.
3. Wessler JD, Grip LT, Mendell J, Giugliano RP. The p-glycoprotein transport system and cardiovascular drugs. *J Am Coll Cardiol* 2013;**61**:2495–2502.
4. Mendell J, Zahir H, Matsushima N, Noveck R, Lee F, Chen S, Zhang G, Shi M. Drug-drug interaction studies of cardiovascular drugs involving p-glycoprotein, an efflux transporter, on the pharmacokinetics of edoxaban, an oral factor xa inhibitor. *Am J Cardiovasc Drugs* 2013;**13**:331–342.
5. Salazar DE, Mendell J, Kastrissios H, Green M, Carrothers TJ, Song S, Patel I, Bocanegra TS, Antman EM, Giugliano RP, Kunitada S, Dornseif B, Shi M, Tachibana M, Zhou S, Rohatagi S. Modelling and simulation of edoxaban exposure and response relationships in patients with atrial fibrillation. *Thromb Haemost* 2012;**107**:925–936.
6. Nieuwlaat R, Prins MH, Le Heuzey JY, Vardas PE, Aliot E, Santini M, Cobbe SM, Widdershoven JW, Baur LH, Levy S, Crijns HJ. Prognosis, disease progression, and treatment of atrial fibrillation patients during 1 year: follow-up of the euro heart survey on atrial fibrillation. *Eur Heart J* 2008;**29**:1181–1189.
7. Ruff CT, Giugliano RP, Braunwald E, Morrow DA, Murphy SA, Kuder JF, Deenadayalu N, Jarolim P, Betcher J, Shi M, Brown K, Patel I, Mercuri M, Antman EM. Association between edoxaban dose, concentration, anti-factor xa activity, and outcomes: An analysis of data from the randomised, double-blind engage AF-TIMI 48 trial. *Lancet* Mar 10 [Epub ahead of print]. 2015; pii: S0140-6736: 61943–61947.
8. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;**3**: 692–694.
9. Steffel J, Braunwald E. Novel oral anticoagulants: focus on stroke prevention and treatment of venous thrombo-embolism. *Eur Heart J* 2011;**32**:1968–1976.
10. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139–1151.
11. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;**365**:883–891.
12. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;**365**:981–992.
13. Liesenfeld KH, Lehr T, Dansirikul C, Reilly PA, Connolly SJ, Ezekowitz MD, Yusuf S, Wallentin L, Haertter S, Staab A. Population pharmacokinetic analysis of the oral thrombin inhibitor dabigatran etexilate in patients with non-valvular atrial fibrillation from the re-ly trial. *J Thromb Haemost* 2011;**9**:2168–2175.
14. Stangier J, Clemens A. Pharmacology, pharmacokinetics, and pharmacodynamics of dabigatran etexilate, an oral direct thrombin inhibitor. *Clin Appl Thromb Hemost* 2009; **15**(Suppl 1):9S–16S.
15. Steffel J, Ruff CT, Goldhaber S, Brunckhorst C. *Stroke prevention in atrial fibrillation*. Bremen: UniMed; 2014.
16. Hankey GJ, Eikelboom JW. Dabigatran etexilate: a new oral thrombin inhibitor. *Circulation* 2011;**123**:1436–1450.