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Edoxaban in atrial fibrillation patients with established coronary artery disease: Insights from ENGAGE AF–TIMI 48

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Abstract

Background: The relative efficacy and safety profile of the oral Factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation and established coronary artery disease (CAD) has not been analyzed.

Materials and methods: In the ENGAGE AF–TIMI 48 trial, two edoxaban regimens were compared with warfarin in 21,105 patients with atrial fibrillation and $CHADS_2 \geqslant 2$. We analyzed the primary trial endpoints (efficacy: stroke or systemic embolic event, safety: International Society on Thrombosis and Haemostasis major bleeding) in patients with versus without CAD, and used interaction testing to assess for treatment effect modification.

Results: The 4510 patients (21.4%) with known CAD were older, more likely male, on aspirin, with lower creatinine clearance and higher $CHADS_2$ and HAS-BLED scores ($p < 0.001$ for each). Treatment with the higher-dose edoxaban regimen (versus warfarin) in patients with known CAD tended to have a greater reduction in stroke/systemic embolic event compared with patients without CAD (CAD: hazard ratio 0.65 (0.46–0.92) versus no CAD: hazard ratio 0.94 (0.79–1.12), *p*-INT 0.062) and also in myocardial infarction (CAD: hazard ratio 0.69 (0.49–0.98) versus no CAD: hazard ratio 1.24 (0.89–1.72), *p*-INT 0.017), while there was a similar reduction in bleeding irrespective of CAD status (hazard ratio 0.81 and 0.80, *p*-INT 0.97). Presence or absence of CAD did not modify the efficacy or safety profile of the lower-dose edoxaban regimen (versus warfarin).

Conclusion: The reduction in ischemic events with the higher-dose edoxaban regimen versus warfarin was greater in patients with CAD, while bleeding was significantly reduced with edoxaban regardless of CAD status. The efficacy and safety profile of the lower-dose edoxaban regimen relative to warfarin was unaffected by CAD status.

Keywords

Atrial fibrillation, coronary artery disease, edoxaban, warfarin, non-vitamin K antagonist oral anticoagulants

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Background

Coronary artery disease (CAD) is a risk factor for stroke in patients with atrial fibrillation and is assigned one point in the CHA_2DS_2-VASc score.[1,2] Patients with atrial fibrillation and CAD are also at increased risk of myocardial infarction

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or cardiovascular death.[3,4] In addition, patients with CAD may require additional therapy with antiplatelet medications and are therefore at higher risk of bleeding. Thus, management of patients can be particularly challenging after stent implantation or an acute coronary syndrome, and the strategy for anticoagulation should be tailored after thorough consideration of the individual patient-specific risks. However, it is well established that the efficacy of anticoagulation is superior to that of antiplatelet agents alone for stroke prophylaxis in atrial fibrillation.[5,6] In addition, warfarin has been shown to reduce the risk of myocardial infarction (MI) post-MI and in patients with atrial fibrillation.[7–9]

Several non-vitamin K antagonist oral anticoagulants (NOACs) have been shown to be non-inferior compared with warfarin in reducing stroke and systemic embolic events (SEE) in patients with atrial fibrillation.[10–13] However, concerns regarding less effective protection from myocardial infarction with dabigatran compared with warfarin in patients with atrial fibrillation have been raised.[14,15]

We performed a subgroup analysis from the ENGAGE AF-TIMI 48 trial to evaluate the relative efficacy and safety profile of edoxaban compared with warfarin in patients with CAD.

Materials and methods

Study population

ENGAGE AF-TIMI 48 was a three arm, randomized, double-blind, double-dummy trial that compared the efficacy and safety of two dose regimens of edoxaban with warfarin.[16,17] Briefly, 21,105 patients with a history of documented atrial fibrillation and a $CHADS_2$ score $\geqslant 2$ were enrolled. Key exclusion criteria were acute coronary syndromes, coronary revascularizations, or stroke within 30 days before randomization; use of dual antiplatelet therapy, a high risk of bleeding, or severe renal dysfunction (creatinine clearance <30 mL/min). Patients were randomized in a 1:1:1 ratio to a higher-dose edoxaban regimen (HDER; 60 mg once daily), a lower-dose edoxaban regimen (LDER; 30 mg once daily), or to warfarin titrated to achieve a target international normalized ratio of 2.0 to 3.0. For patients in either edoxaban arm, the dose was halved if any of the following characteristics were present at the time of randomization or during the study: estimated creatinine clearance of $\leqslant 50$ mL/min, a body weight of 60 kg or less, or the concomitant use of verapamil, quinidine, or dronedarone (potent P-glycoprotein inhibitors). Single antiplatelet therapy (SAPT) was administered as directed by the treating physician; aspirin $\leqslant 100$ mg daily was strongly encouraged. If a clinical indication for dual antiplatelet therapy arose after randomization, the study drug was temporarily interrupted, but open-label vitamin K antagonist was permitted. The protocol and amendments were approved by the ethics committee at each participating center and all the patients provided written informed consent.

This prespecified analysis from ENGAGE AF–TIMI 48 studied the efficacy and safety of the HDER (the approved edoxaban regimen) and LDER compared with warfarin in patients with established CAD and atrial fibrillation. CAD was defined as presence at baseline of at least one of the following: 1) prior myocardial infarction, 2) prior coronary revascularization (i.e. percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG)), or 3) coronary stenosis $>50\%$ as reported by the investigator. Three sensitivity analyses were performed that: 1) used a broader CAD definition that also included patients with a history of angina, 2) restricted the definition to prior myocardial infarction only, and 3) restricted the definition to coronary revascularizations excluding all patients with prior MI (see Supplementary Material online).

In addition, an exploratory analysis was performed to assess the efficacy and safety of edoxaban in patients stratified by use of SAPT at three months. Given that a substantial proportion of patients (n=498; 7.46%) discontinued SAPT shortly after entering the ENGAGE AF–TIMI 48 trial and starting anticoagulant therapy, we compared SAPT with no SAPT beginning three months after randomization, using a similar approach to that previously reported.[18] Therefore, patients with events (death, stroke, SEE, or major bleeding) before the three month visit were excluded from this exploratory analysis.

Endpoints

The same endpoints as previously described in the ENGAGE AF–TIMI 48 trial were used for the present subgroup analysis.[16,17] The primary efficacy endpoint was time to the first component of the composite of stroke or SEE; the principal safety endpoint was time to major bleeding (as defined by the International Society on Thrombosis and Haemostasis).[19] Secondary efficacy and safety endpoints were major adverse cardiovascular events (MACE; defined as MI, stroke, SEE, or death due to cardiovascular cause including bleeding), their individual components, any stroke, any intracranial bleeding, life-threatening or fatal bleeding, and gastrointestinal bleeding. In addition, a net clinical outcome consisting of stroke, SEE, major bleeding, and death from any cause was assessed. The definition of MI was modified from the Universal definition of myocardial infarction recommended by the Joint ESC/ACCF/AHA/WHF Task Force[20] and details of our definition have been published.[16,17] An independent clinical endpoint committee adjudicated all events, blinded to treatment assignment.

Pharmacokinetic and pharmacodynamic assessment

Plasma edoxaban concentration and anti-Factor Xa (FXa) activity were measured in trough blood samples, collected one month after randomization, as previously described.[21] Edoxaban concentrations were measured by Quintiles

Bioanalytical and ADME Laboratories (formerly Advion BioServices (Ithaca, NY, USA)) using a validated turbo ion spray liquid chromatography mass spectrometry/mass spectrometry method. Anti-FXa activity was measured by the Rotachrome Heparin assay on the Stago STAR Evolution platform (TIMI Clinical Trials Laboratory, Boston, MA, USA).[21] The pharmacodynamic effect of warfarin was assessed using the Rosendaal method of calculating the time in the therapeutic range (TTR).[22]

Statistical analysis

Baseline characteristics are summarized using means (and standard deviation) or medians (and quartiles) as appropriate. Outcomes are presented as total numbers and as annualized event rates, and are examined using Cox regression models. To assess the risk of CAD patients compared with non-CAD patients, Cox regression models were adjusted for age, gender, body mass index, quartiles of creatinine, history of hypertension, dyslipidemia, diabetes, stroke or transient ischemic attack, congestive heart failure, smoking status, type of atrial fibrillation (paroxysmal, persistent, permanent), race, region, history of increased risk of falling, history of neuropsychiatric disease, hepatic disease, non-intracranial hemorrhage (ICH) bleeding, alcohol intake, and antiplatelet therapy. The proportional hazards assumption was confirmed using statistical tests and visual inspection based on the scaled Schoenfeld residuals.[23] Statistical significance was assessed at a nominal alpha level of 0.05. All reported p values are two-sided and no adjustments for multiple testing were performed. Statistical analyses were otherwise carried out using SAS software, Version 9.2.

Results

Study population

Of the 21,105 patients from the ENGAGE AF-TIMI 48 trial, 4510 patients (21.4%) were diagnosed with clinically established CAD at baseline. Among those, 2647 (58.7%) had prior coronary revascularization (prior PCI: 1440 patients; CABG: 1456 patients), 1190 (26.4%) had known medically treated coronary stenosis (>50%), and 2433 patients (53.9%) had prior MI (categories were not mutually exclusive; Supplementary Figure S1). Details on CAD status were missing for three patients; 17 patients were reported to have CAD but did not have any further information available. Compared with patients without clinically evident CAD (n=16,592), patients with established CAD were more likely to be older, male, treated with aspirin, have lower eGFR, higher TIMI atrial fibrillation risk score,[24] $CHADS_2$ and HAS-BLED scores and more frequently had paroxysmal atrial fibrillation ($p<0.001$ for each; Table 1). The baseline characteristics were generally well-balanced across the randomized treatment arms in patients with CAD and in patients without CAD (Supplementary Table S1). The median TTR (70.0 (interquartile range (IQR) 57.8–78.6) *vs*. 68.1 (IQR 56.3–77.0); $p = 0.004$), trough edoxaban concentration (HDER: 36.4 *vs*. 32.5; LDER: 17.9 *vs*. 16.3, both $p < 0.001$) and anti-FXa activity (HDER: 0.71 *vs*. 0.58, $p < 0.001$; LDER:0.36 *vs*. 0.31, $p = 0.05$) were significantly higher in the group with CAD versus without CAD (Table 2). The trough edoxaban concentrations were significantly higher in the CAD group even after stratification by dose-reduction status.

Outcomes by presence of established CAD in the warfarin arm

To compare the outcomes between the CAD and no-CAD groups, we assessed patients randomized to warfarin to eliminate any potential treatment interaction (Figure 1). The observed (unadjusted) annualized event rates were significantly higher for MI (CAD: 1.97 *vs*. no CAD: 0.43, $p < 0.001$), MACE (CAD 7.40 *vs*. no CAD 4.34, $p < 0.001$), all-cause mortality (CAD: 6.30 *vs*. no CAD: 3.82, $p < 0.001$), cardiovascular death (CAD: 4.63 *vs*. no CAD: 2.77, $p < 0.001$), and major bleeding (CAD: 4.45 *vs*. no-CAD 3.17, p= 0.009) (Figure 1; Supplementary Tables S2–S4). The rate was numerically, but not significantly, higher in patients with CAD for stroke/SEE (CAD 2.12 vs. no CAD 1.72, p=0.12). Patients with CAD experienced similar annual rates of ICH (CAD: 0.88 vs. no CAD 0.84, p= 0.98), and fatal or life threatening bleeding (CAD: 1.22 *vs*. no CAD 1.15, p= 0.89) as those without CAD.

After multivariable adjustment for imbalances in patient characteristics, the presence of CAD remained independently associated with significantly higher risks of SEE (adjusted hazard ratio (HR_{adj}) 2.72 (1.10–6.73)), MACE (HR_{adj} 1.42 (1.21–1.67)), MI (HR_{adj} 3.27 (2.21–4.83)), cardiovascular death (HR_{adj} 1.37 (1.12–1.67)), and all-cause death (HR_{adj} 1.37 (1.16–1.63)) (Figure 1).

Outcomes by randomized treatment and presence of CAD

HDER versus warfarin. While the risk of stroke/SEE was numerically lower in the HDER group regardless of CAD status, patients with CAD tended to have an even greater reduction in stroke/SEE with HDER (CAD: hazard ratio 0.65 (0.46–0.92) *vs*. no-CAD: hazard ratio 0.94 (0.79-–1.12), p-INT 0.062; Figure 2). Patients with CAD had a significantly greater reduction in myocardial infarction in the HDER group (versus warfarin) compared with patients without CAD (CAD: hazard ratio 0.69 (0.48–0.98) *vs*. no CAD: hazard ratio 1.24 (0.89–1.71); p-INT 0.017; Figure 3). Patients randomized to HDER exhibited a similar reduction in the risk of major bleeding compared with warfarin regardless of CAD status (CAD: hazard ratio 0.81 (0.63–1.04) *vs*. no-CAD: hazard ratio 0.80 (0.69–0.93), p-INT 0.97). HDER was associated with an increase in gastrointestinal bleeding irrespective of CAD status (CAD: hazard ratio 1.19 (0.84–1.67) *vs*. no-CAD: 1.26 (1.00–1.60),

p-INT 0.76). No other treatment effect modifications due to CAD status were found for other endpoints (*p*-INT >0.10), including the net clinical outcome (*p*-INT 0.74).

There was a consistent treatment effect of HDER compared with warfarin regardless of the presence of concomitant SAPT (Supplementary Figure S3). In patients

Table 1. Baseline characteristics of patients stratified by CAD status.

	No CAD *n*=16,592	CAD *n*=4510	
Age, mean (SD)	70.2 (9.6)	72.2 (8.70)	*
Female	6991 (42.1%)	1048 (23.2%)	*
Weight, kg			
Mean (SD)	83.2 (20.4)	86.6 (19.2)	*
>60 kg	14,770 (89.0%)	4249 (94.2%)	*
Creatinine clearance, mL/min per 1.73 m^2, mean (SD)	77.2 (31.7)	73.0 (29.5)	*
Smoking (active)	1201 (7.2%)	351 (7.8%)	*
Hypertension	15,475 (93.3%)	4276 (94.8%)	*
Dyslipidemia	7714 (46.5%)	3341 (74.1%)	*
Carotid artery disease	735 (4.4%)	561 (12.4%)	*
Peripheral artery disease	443 (2.7%)	398 (8.8%)	*
Congestive heart failure	9278 (55.9%)	2845 (63.1%)	*
Diabetes mellitus	5620 (33.9%)	2002 (44.4%)	*
Stroke/TIA	4808 (29.0%)	1165 (25.8%)	*
History of bleeding	1466 (8.8%)	614 (13.6%)	*
Type of AF, paroxysmal	4111 (24.8%)	1253 (27.8%)	*
$CHADS_2$			
Mean (SD)	2.80 (0.95)	3.00 (1.04)	*
>3	3539 (21.3%)	1229 (27.3%)	*
CHA_2DS_2VASc			
Mean (SD)	4.14 (1.36)	5.03 (1.27)	*
>4	5971 (36.0%)	2807 (62.2%)	
CHA_2DS_2(V)ASc without 'V'			
Mean (SD)	3.94 (1.26)	4.03 (1.27)	*
>4	4985 (30.0%)	1422 (31.5%)	*
HAS-BLED			
Mean (SD)	2.42 (0.94)	2.82 (0.99)	*
>3	7036 (42.4%)	2764 (61.3%)	*
TIMI AF risk score			
Low, 0–6	11,175 (69.7%)	1994 (45.9%)	*
Intermediate, 7–9	4333 (27.0%)	1824 (42.0%)	*
High, >10	517 (3.2%)	527 (12.1%)	*
Single-antiplatelet therapy at randomization	4421 (26.6%)	2256 (50.0%)	*
Aspirin at randomization	4144 (25.0%)	2035 (45.1%)	*
Dose reduction at randomization	4217 (25.4%)	1138 (25.2%)	

*All *p*-values <0.001, except for CHA_2DS_2(V)ASc without 'V' >4 (*p*=0.054), and dose reduction (*p*=0.80).
CAD: coronary artery disease; TIA: transient ischemic attack; AF: atrial fibrillation.

Table 2. Trough plasma edoxaban concentration and anti-FXa activity stratified by CAD and dose regimen.
(a) All edoxaban dose groups.

	HDER			LDER		
	CAD	No CAD	*p*-value	CAD	No CAD	*p*-value
Edoxaban concentration, ng/mL	*n* = 684	*n* = 2639		*n* = 754	*n* = 2701	
Median (IQR)	36.4 (20.5–63.9)	32.5 (17.7–55.6)	<0.001	17.9 (10.8–30.7)	16.3 (8.8–28.9)	<0.001
Anti-FXa activity, IU/mL	*n* = 317	*n* = 1136		*n* = 357	*n* = 1055	
Median (IQR)	0.71 (0.42–1.15)	0.58 (0.33–1.01)	<0.001	0.36 (0.22–0.56)	0.31 (0.20–0.52)	0.05

Table 2. (Continued)

(b) No dose reduction at randomization.

	HDER			LDER		
	CAD	No CAD	*p*-value	CAD	No CAD	*p*-value
Edoxaban concentration, ng/mL	*n* = 524	*n* = 1978		*n* = 555	*n* = 2056	
Median (IQR)	39.8 (22.3–68.2)	35.1 (18.9–60.4)	0.004	20.9 (11.9–34.7)	17.9 (9.7–31.8)	0.002
Anti-FXa activity, IU/mL	*n* = 249	*n* = 880		*n* = 281	*n* = 821	
Median (IQR)	0.75 (0.45–1.24)	0.6 (0.36–1.08)	0.001	0.38 (0.23–0.57)	0.33 (0.21–0.57)	0.28

(c) Dose reduction at randomization.

	HDER			LDER		
	CAD	No CAD	*p*-value	CAD	No CAD	*p*-value
Edoxaban concentration, ng/mL	*n* = 160	*n* = 661		*n* = 199	*n* = 645	
Median (IQR)	30.1 (16.3–50.1)	26.2 (14.3–42.9)	0.028	13.5 (8.5–22.1)	12.1 (7.1–20.3)	0.010
Anti-FXa activity, IU/mL	*n* = 68	*n* = 256		*n* = 76	*n* = 234	
Median (IQR)	0.60 (0.29–0.90)	0.5 (0.30–0.82)	0.44	0.32 (0.20–0.55)	0.26 (0.17–0.39)	0.032

CAD: coronary artery disease; FXa: Factor Xa; HDER: higher-dose edoxaban regimen; IQR: interquartile range; LDER: lower-dose edoxaban regimen.

with concomitant SAPT (92% of which was aspirin), HDER tended to reduce MIs to a greater degree in patients with CAD compared with patients without established CAD (CAD: hazard ratio 0.66 (0.39–1.12) *vs*. no CAD 1.42 (0.70–2.88); *p*-INT 0.087; Supplementary Figure S2).

LDER versus warfarin. Treatment with LDER as compared with warfarin resulted in similar risks of stroke/SEE (CAD: hazard ratio 1.04 (0.77–1.40 *vs*. no-CAD: hazard ratio 1.16 (0.98–1.37); *p*-INT 0.53). There were significant reductions in major bleeding (CAD: hazard ratio 0.45 (0.33–0.60) *vs*. no-CAD: hazard ratio 0.48 (0.40–0.57); *p*-INT 0.67) that were of a similar magnitude irrespective of CAD status. LDER was associated with a significant reduction in gastrointestinal bleeding irrespective of CAD status (hazard ratio 0.51 (0.34–0.78) *vs*. no-CAD: 0.74 (0.57–0.97); *p*-INT 0.15). No significant interactions in other outcomes were observed for the comparison of the LDER versus warfarin stratified by CAD status or by concomitant SAPT use (Figure 2; Supplementary Figure S2).

Sensitivity analyses using alternative definitions of CAD

The findings of greater beneficial effects of HDER over warfarin in reducing MI and the composite of stroke/SEE in the CAD cohort prompted the conduct of several post-hoc sensitivity analyses using different definitions of coronary artery disease. Although the interactions did not meet significance (each *p*-INT >0.1), the directional trend and the point estimates for myocardial infarction were similar when: 1) broadening the CAD definition to include patients with a history of angina (CAD: hazard ratio 0.85 *vs*. no-CAD: 1.07, *p*-INT 0.36; Supplementary Figure S4), 2) restricting the definition to prior myocardial infarction (prior MI: hazard ratio 0.71 *vs*. no prior MI: 1.05; *p*-INT 0.17; Supplementary Figure S5), and 3) stratifying by prior revascularization (excluding all patients with prior MI) (prior revascularization: hazard ratio 0.80 *vs*. no prior revascularization: 1.13; *p*-INT 0.30; Supplementary Figure S6). Similar point estimates were also observed for the primary efficacy outcome of stroke/SEE in all three sensitivity analyses (Supplementary Figures S4–S6).

Discussion

The principal findings of this analysis were an interaction between CAD status and HDER treatment for myocardial infarction (*p*-INT 0.017) and a trend in the interaction for stroke/SEE (*p*-INT 0.062), suggesting larger reductions of these events in patients treated with HDER versus warfarin in patients with CAD compared with patients without CAD. The presence or absence of CAD did not modify the significant reduction in major bleeding observed with HDER. In addition, CAD status did not have any effect on the efficacy or safety of LDER.

The reduction of MIs in HDER-treated patients with CAD was unexpected since warfarin reduces MI[7–9] and the TTR was even higher in warfarin-treated patients with CAD (versus no CAD). However, unlike warfarin, edoxaban can penetrate thrombi that may be present in some patients with CAD, thereby enabling a more effective inhibition of both circulating and bound FXa in the prothrombinase complex.[25,26] This notion, supported by higher edoxaban serum concentrations in patients with CAD, may have contributed to the observed treatment-subgroup

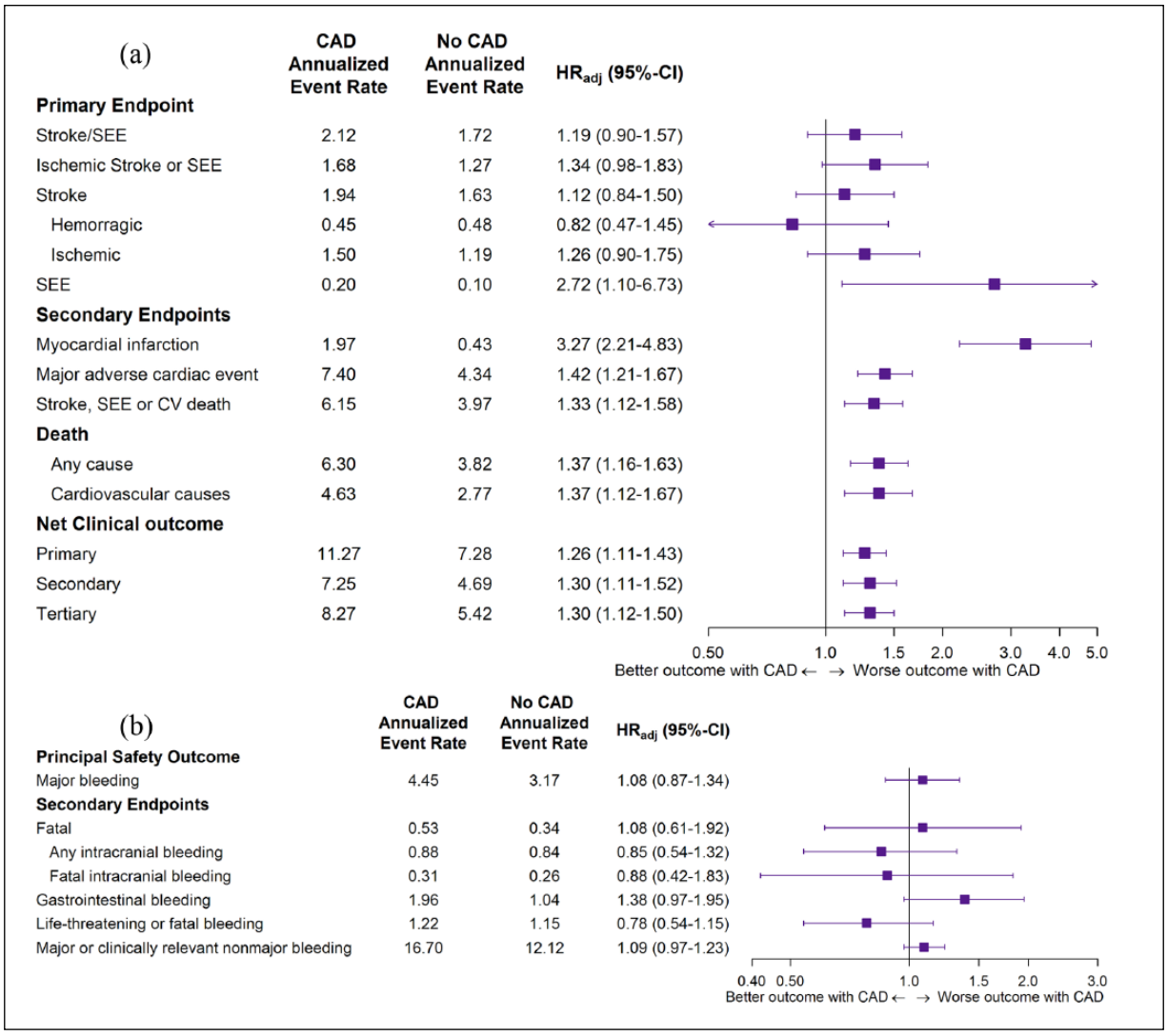

Figure 1. Efficacy (a) and safety (b) outcomes in the warfarin treatment group for established CAD versus not evident CAD.
Hazard ratios were adjusted for age, gender, body mass index, quartiles of creatinine, history of hypertension, dyslipidemia, diabetes, stroke or transient ischemic attack, congestive heart failure, smoking status, type of atrial fibrillation, race, region, history of increased risk of falling, history of neuropsychiatric disease, hepatic disease, non-intracerebral hemorrhage bleed, alcohol, and medication. Major adverse cardiac events are defined as myocardial infarction, stroke, systemic embolic event, or death due to cardiovascular cause including bleeding. Definition of net clinical outcome: primary: stroke, systemic embolic event, major bleeding, and death from any cause; secondary: disabling stroke, life-threatening bleeding, or death from any cause; tertiary: stroke, systemic embolic event, life-threatening bleeding or death from any cause.
CAD: coronary artery disease; CI: confidence interval; CV: cardiovascular; HR_{adj}: adjusted hazard ratio; SEE: systemic embolic event.

interactions with HDER, and may explain the lack of a signal for LDER (which achieved a 50% lower concentration). In addition, since bleeding is a well-known cause of cessation and underdosing of anticoagulation, the significant reduction of major bleeding with edoxaban (compared with warfarin) led to fewer interruptions of anticoagulation,[16,27] thus resulting in a greater duration of effective cardiovascular protection from thrombotic events in patients randomized to edoxaban. Furthermore, there is growing evidence that bleeding may provoke a prothrombotic state and represent an independent risk factor for myocardial infarction, stroke, and death.[28–30] Other potential explanations for the enhanced benefit of edoxaban in patients with CAD may be found in edoxaban's favorable pharmacodynamic and pharmacokinetic properties, including the rapid onset of action, lack of significant food interactions, and less potential for drug interactions.[31–34]

While the absolute risk reduction of MI was considerably greater in patients with CAD (0.6% per year favoring HDER) compared with patients without CAD (0.1% per year favoring warfarin), the annualized event rate of MI in the no-CAD group was substantially lower. The low incidence of myocardial infarction in the no-CAD group therefore magnifies a relative comparison (such as a hazard ratio) as a measure of effect size. Sensitivity analyses of patients stratified by three different definitions of prior

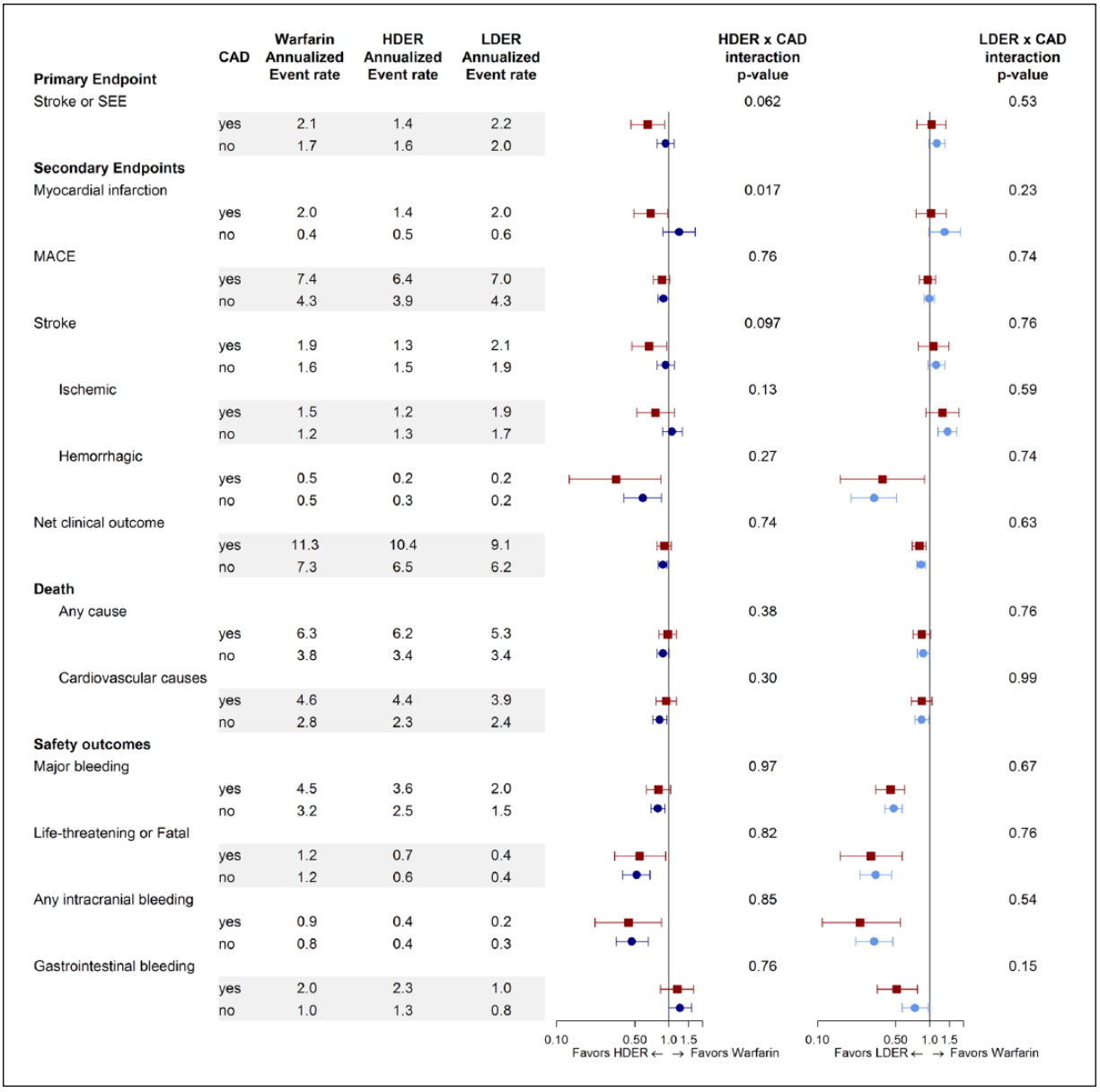

Figure 2. Efficacy and safety of edoxaban versus warfarin stratified by prior CAD.
MACEs were defined as myocardial infarction, stroke, SEE, or death due to cardiovascular cause including bleeding. The net clinical benefit was a composite of stroke, systemic embolic event, major bleeding, and all-cause mortality.
CAD: coronary artery disease: HDER: higher-dose edoxaban regimen: LDER: lower-dose edoxaban regimen; MACE: major adverse coronary event; SEE: systemic embolic event.

CAD also support the notion of the consistent profile of edoxaban in patients without CAD. Of note, in the high-risk CAD patient cohort, the hazard ratios (and the absolute risk reductions) are nearly identical whether the population is stratified by presence of CAD, by MI, or by prior revascularization. An exploratory analysis restricted to patients on concomitant antiplatelet therapy found qualitatively similar results. The efficacy and safety profile of edoxaban relative to warfarin was otherwise not modified by CAD status.

While our data support the notion that HDER is at least as effective in a high-risk population with CAD and atrial fibrillation, a subgroup analysis from ROCKET-AF pointed in the opposite direction. Significant treatment interactions were observed for all-cause mortality and the primary safety endpoint of major and non-major clinical relevant bleeding, suggesting that patients with prior myocardial infarction had a less favorable balance of efficacy and safety with rivaroxaban relative to warfarin than did patients without a prior myocardial infarction.[35]

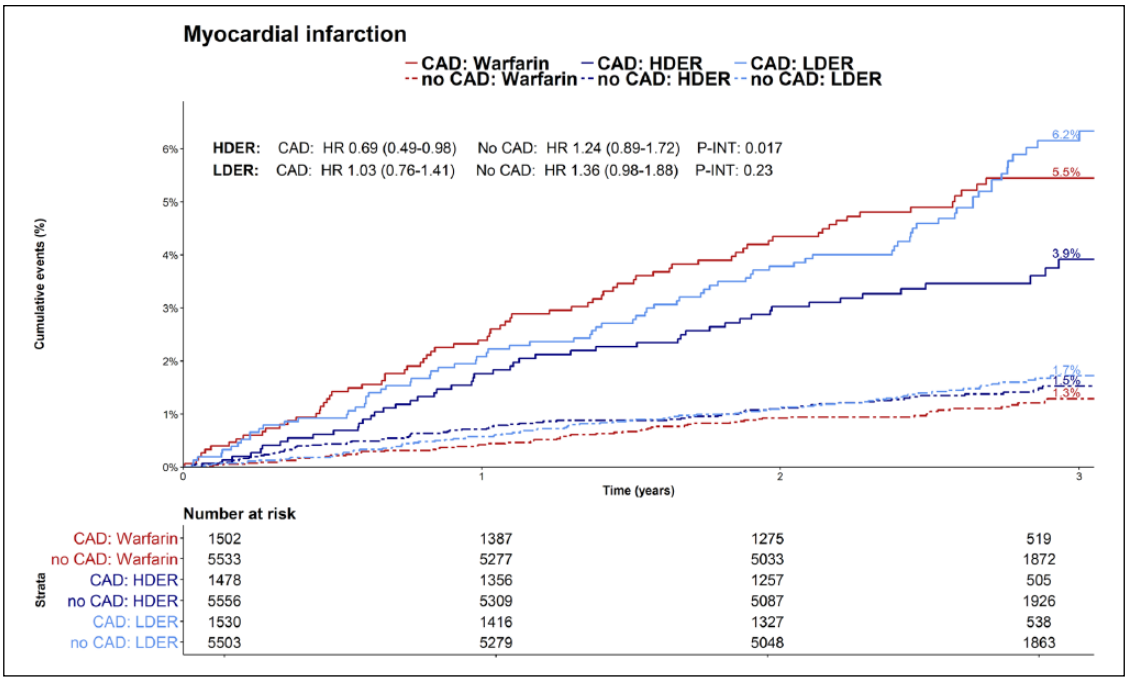

Figure 3. Kaplan–Meier curve and the corresponding Kaplan–Meier event rates at three years for myocardial infarction stratified by treatment and presence of established coronary artery disease.
CAD: coronary artery disease; HDER: higher-dose edoxaban regimen; HR: hazard ratio; LDER: lower-dose edoxaban regimen.

Similar subgroup analyses with apixaban and dabigatran from the ARISTOTLE and RE-LY trial, respectively, showed no treatment-CAD subgroup interactions for the major efficacy and safety outcomes.[15,36] However, it should be highlighted that the subgroup analysis from ROCKET-AF examined the efficacy and safety of rivaroxaban in patients with prior myocardial infarction (and not in the broader group of patients with CAD). The proportions of patients with prior myocardial infarction (17.3 *vs*. 11.5%) and $CHADS_2$ score 4–6 (43.4% *vs*. 22.6%) were higher in ROCKET-AF compared with ENGAGE AF–TIMI 48, underscoring the differences in patient populations across the NOAC trials. As such, this analysis does not allow to infer on comparisons between edoxaban and other NOACs[15,35,36] that could only be established by prospective randomized controlled trials with head-to-head comparisons.

The findings of the ATLAS ACS 2–TIMI 51 trial[37] and the COMPASS trial[38] suggest that very low-dose NOACs might also have beneficial effects in CAD patients without atrial fibrillation. While LDER tended to have less favorable effects in our study, it was compared with warfarin, which possesses protective effects (reducing ischemic events) at a cost of an increase in bleeding events. In contrast, there was no anticoagulant in the comparator arms of ATLAS ACS 2–TIMI 51 or COMPASS trials. In addition, patients in these two trials were younger, received a considerably lower dosage of NOAC, and use of concomitant antiplatelet therapy was determined by the study protocols. Thus, the totality of evidence in patients with or without atrial fibrillation, including older data with warfarin and newer data with NOACs, supports a protective effect with oral anticoagulation in patients with CAD.

Limitations

In addition to the known limitations of subgroup analyses, further aspects should be highlighted. First, the low frequency of several outcomes resulted in low power, thereby reducing the reliability of the statistical tests. Due to the exploratory nature of this analysis, no adjustments for multiple testing were performed, therefore increasing the chances of a Type I error.

In our study, patients without established CAD had a median age of 72 years and a $CHADS_2$ score ⩾2. Therefore, preclinical CAD is highly probable. However, a subgroup analysis from the epidemiological Reasons for Geographic and Racial Differences in Stroke (REGARDS) study that compared the risk of myocardial infarction in patients with versus without atrial fibrillation in patients with average age 62 years without prevalent CAD showed an incidence rate of MI of 1.2% per year (*vs*. 0.5% in our study) in patients with atrial fibrillation.[3] Of note, the American Heart Association's report on Heart Disease and Stroke statistics reports an overall incidence of MIs in 65–74 year old subjects of approximately 0.7% (with considerable differences in sex and race),[39] which is similar to the rate in our population without known CAD.

Conclusion

Although patients with atrial fibrillation and known CAD are at higher risk of MI and death, the absolute and proportional reductions of MI in patients treated with HDER as compared with warfarin were significantly greater among patients with CAD than among those without CAD. In addition, the reduction in myocardial ischemic events with edoxaban versus warfarin was greater in patients with atrial fibrillation and CAD, while bleeding was reduced regardless of CAD status. The treatment effects of HDER relative to warfarin on stroke/SEE and bleeding were otherwise consistent regardless of the presence or absence of prior CAD. These observations suggest that in patients with CAD who require an oral anticoagulant for atrial fibrillation, HDER may be a preferred agent compared with warfarin.

Conflict of interest

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