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Edoxaban Versus Warfarin in Patients With Atrial Fibrillation and History of Liver Disease

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ABSTRACT

BACKGROUND Patients with liver disease have increased risk of thrombosis and bleeding but are typically excluded from trials of direct oral anticoagulant agents.

OBJECTIVES This study evaluated the pharmacokinetics (PK), pharmacodynamics (PD), clinical efficacy and safety of edoxaban versus warfarin in patients with atrial fibrillation (AF) and history of liver disease.

METHODS ENGAGE AF-TIMI 48 (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis In Myocardial Infarction Study 48) was a randomized, double-blind trial comparing edoxaban with warfarin in patients with AF followed for 2.8 years. History of liver disease was defined as investigator-reported liver disease or >2-fold transaminase elevation at randomization. The primary efficacy and safety endpoints of stroke or systemic embolic event (SSEE) and major bleeding were assessed stratified by history of liver disease. PK/PD assessments of edoxaban included endogenous and extrinsic factor Xa activity and edoxaban concentration.

RESULTS Among 21,105 patients, 1,083 (5.1%) had a history of liver disease; they had a higher prevalence of many comorbidities. The adjusted risks of SSEE were similar (adjusted hazard ratio [HR_{adj}]: 0.90; 95% confidence interval [CI]: 0.67 to 1.22; $p = 0.50$), but major bleeding was more common in patients with liver disease (HR_{adj}: 1.38; 95% CI: 1.10 to 1.74; $p = 0.005$). There were no significant differences in PK/PD assessment of edoxaban in patients with versus without liver disease. The HRs for higher-dose edoxaban versus warfarin for SSEE were 0.86 (95% CI: 0.73 to 1.01) in patients without and 1.11 (95% CI: 0.54 to 2.30) with liver disease (p for interaction [p_{int}] = 0.47), major bleeding 0.80 (95% CI: 0.70 to 0.91) in patients without and 0.91 (95% CI: 0.56 to 1.47) with liver disease ($p_{int} = 0.63$). There were no significant differences in hepatic adverse events between the 2 treatment groups.

CONCLUSIONS Among patients with AF receiving oral anticoagulation, bleeding, but not thromboembolic events, was increased in patients with liver disease. A history of liver disease did not alter the relative efficacy and safety of edoxaban compared with warfarin. Hepatic adverse events were similar between edoxaban and warfarin.
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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

ALT = alanine aminotransferase

AST = aspartate aminotransferase

CI = confidence interval

CV = cardiovascular

DOAC = direct oral anticoagulant

FXa = factor Xa

HDER = higher-dose edoxaban regimen

HR = hazard ratio

INR = international normalized ratio

LDER = lower-dose edoxaban regimen

SSEE = stroke or systemic embolic events

ULN = upper limit of normal

Liver disease is a major public health problem globally, with more than 1 million deaths every year (1). In patients with liver disease, cardiovascular (CV) disease is the most common cause of death (2). Liver disease is also associated with an increased risk of atrial fibrillation (AF) independent of traditional risk factors (3,4). Therefore, patients with liver disease often have AF in addition to other risk factors for stroke and require oral anticoagulation. However, due to decreased production of coagulation factors, thrombocytopenia, and increased fibrinolysis in liver disease (5), the use of oral anticoagulation is complicated by increased bleeding.

Direct oral anticoagulant agents (DOACs) are effective in preventing stroke and thromboembolism in the general population of patients with AF, however, randomized clinical trials of DOACs generally have excluded patients with liver disease (6–8). All DOACs undergo significant hepatobiliary metabolism; thus, liver dysfunction may increase drug levels, augment anticoagulation, and heighten bleeding risk. The efficacy and safety of DOACs in patients with AF who have coexistent liver disease are not known.

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Edoxaban, a direct oral factor Xa (FXa) inhibitor, is cleared by the liver (up to 50% of the absorbed drug) and the kidneys (50%) (9). In ENGAGE AF-TIMI 48 (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction Study 48), the efficacy and safety of 2 dosing regimens of edoxaban were compared with warfarin in patients with AF at moderate to high risk of stroke (10,11). The higher-dose edoxaban regimen (HDER) (10) was found to be noninferior to warfarin in preventing the primary efficacy endpoint of stroke or systemic embolic events (SSEE) and was associated with significantly lower rates of the principal safety endpoint of major bleeding, as defined by the International Society on Thrombosis and Haemostasis (ISTH), intracranial hemorrhage, and CV mortality, resulting in its regulatory approval for preventing stroke or systemic embolism in AF (10).

The current regulatory guidance for the use of edoxaban and other DOACs in patients with liver disease is based on small pharmacokinetics (PK) and pharmacodynamics (PD) studies (12–15). The U.S. Food and Drug Administration recommends the use of edoxaban without dose adjustment in patients with mild hepatic impairment (Child-Pugh A) and contradicts its use in patients with moderate or severe hepatic impairment (Child-Pugh B or C) (5,16). In this analysis, we investigate the PK, PD, efficacy, and safety of edoxaban compared with warfarin in patients with and without history of liver disease in ENGAGE AF-TIMI 48.

METHODS

STUDY POPULATION. ENGAGE AF-TIMI 48, reported in detail previously (10), enrolled 21,105 patients ≥21 years of age with AF in the past 12 months and a $CHADS_2$ score ≥2. Patients were ineligible if they had active liver disease, persistent (confirmed by repeat assessment within a week) elevation in liver enzymes (alanine aminotransferase [ALT]/aspartate aminotransferase [AST] ≥2× upper limit of normal [ULN] or alkaline phosphatases ≥2× ULN) or total bilirubin ≥1.5× ULN during screening, history of positive hepatitis B antigen or hepatitis C antibody, alcohol dependence within the past 1 year, CrCl <30 ml/min, a high risk of bleeding, platelet count <100,000/μl, moderate-to-severe mitral stenosis, mechanical heart valve, planned use of dual antiplatelet therapy, or other indication for anticoagulation therapy during the study period. The median follow-up was 2.8 years. Written informed consent was obtained from all study participants. History of liver disease was defined as presence of prior liver disease as determined by the site investigator, or presence of elevated liver enzymes (ALT/AST ≥2× ULN) at randomization.

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RANDOMIZATION AND STUDY DRUGS. Patients were randomly assigned in a 1:1:1 ratio, to receive HDER (60 mg daily, or 30 mg daily in patients with CrCl 30 to 50 ml/min, body weight ≤60 kg, or concomitant use of potent P-glycoprotein inhibitors), a lower-dose edoxaban regimen (LDER) (30 mg daily, or 15 mg daily if dose reduction was required), or warfarin dose adjusted to an international normalized ratio (INR) of 2.0 to 3.0.

OBJECTIVES. The aims of this analysis were the following: 1) to compare the rates of SSEE and bleeding in patients with versus without liver disease; 2) to compare the PK and PD of edoxaban and warfarin in patients with versus without liver disease to provide mechanistic insights into the relative efficacy and safety of edoxaban versus warfarin; 3) to examine interactions for efficacy, safety, and net outcomes between edoxaban and warfarin in patients with versus without liver disease; and 4) to compare the hepatic safety of edoxaban versus warfarin.

PK AND PD EVALUATION. Baseline endogenous FXa activity was assessed before administration of the first dose of study drug. The peak and trough percentages of inhibition of endogenous FXa activity were measured at day 29 after randomization at the TIMI Clinical Trials Laboratory in Boston, Massachusetts, using a validated assay described previously (17). In addition, trough extrinsic FXa activity and edoxaban plasma concentrations were assayed on day 29 as previously described (18).

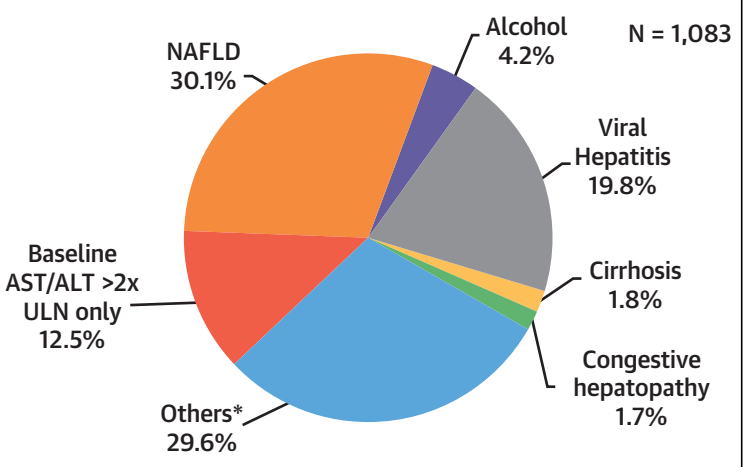
Warfarin PD was assessed by INR measured at least monthly using a point-of-care device. The time in the therapeutic range on warfarin was estimated by means of linear interpolation by individually calculating the time in the therapeutic range for each patient (19).

HEPATIC SAFETY ASSESSMENT. Severity of liver injury was assessed by monitoring of liver function abnormalities on days 1, 8, 15, 29, and then monthly till 1 year, and thereafter every 3 months (AST, ALT, total bilirubin, and alkaline phosphatase levels) using criteria developed by Council for International Organizations of Medical Sciences hepatic experts. Definitions of the severity of liver injury were pre-specified and are described in the protocol (11,18) (Online Table 1). The severity of liver injury was defined in a mutually exclusive and hierarchical fashion. Potentially serious hepatic events were adjudicated by 2 independent hepatologists, who were unaware of treatment assignment based on pre-specified criteria.

STATISTICAL ANALYSIS. In the baseline characteristics, continuous variables are reported as mean ± SD, or median with interquartile range, and categorical variables as frequency and percentage. Differences in baseline characteristics of patients with and without liver disease were tested with the Kruskal-Wallis test for continuous variables and Pearson chi-square test for categorical variables. Frequencies of liver disease etiologies are reported for patients with liver disease. Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) comparing efficacy and safety outcomes by presence or absence of liver disease were calculated using Cox proportional hazards modeling with randomized treatment as a covariate, in addition to the following baseline characteristics: age, sex, body mass index, quartiles of creatinine, history of hypertension, history of dyslipidemia, history of diabetes, history of smoking, history of stroke or transient ischemic attack, history of heart failure, type of AF, race, region, history of increased risk of falling, history of neuropsychiatric disease, history of coronary artery disease, history of nonintracranial hemorrhage, alcohol intake, and medications (antiplatelet agents or nonsteroidal anti-inflammatory drugs). The Kruskal-Wallis test was used to compare endogenous and exogenous FXa activity and edoxaban levels in patients with versus without liver disease.

All efficacy and net clinical outcome analyses of edoxaban versus warfarin were performed on an intention-to-treat basis using Cox proportional hazard modeling with randomized treatment as a

FIGURE 1 Distribution of Liver Disease



*Others = history of abnormal laboratory liver tests (6.3%), liver disease with involvement of the gall bladder and biliary system (4.5%), benign hyperbilirubinemia or Gilbert's syndrome (3.3%), drug-induced liver injury (2.9%), cystic disease of the liver (1.8%), jaundice or hepatic encephalopathy (1.4%), chronic hepatopathy (1.2%), autoimmune hepatitis, hemochromatosis, liver abscess, hepatic hemangioma, history of liver transplant, or history of liver disease without documentation of a specific etiology (7.9%). ALT = alanine aminotransferase; AST = aspartate aminotransferase; NAFLD = nonalcoholic fatty liver disease; ULN = upper limit of normal.

TABLE 1 Baseline Characteristics of Patients According to History of Liver Disease

	No Liver Disease (n = 20,022)	Liver Disease (n = 1,083)	p Value*
Age, yrs	70.7 ± 9.4	68.4 ± 9.7	**<0.001**
Female	7,655 (38.2)	385 (35.5)	0.07
BMI, kg/m^2	29.4 ± 5.9	29.9 ± 6.3	**0.014**
White	16,294 (81.4)	773 (71.4)	**<0.001**
Regions			**<0.001**
North America	4,527 (22.6)	154 (14.2)	
Latin America	2,605 (13.0)	56 (5.2)	
Western Europe	3,114 (15.6)	122 (11.3)	
Eastern Europe	6,690 (33.4)	454 (41.9)	
Asia-Pacific and South Africa	3,086 (15.4)	297 (27.4)	
Patients meeting dose reduction criteria	5,112 (25.5)	244 (22.5)	**0.027**
Aspirin use at randomization	5,865 (29.2)	315 (29.1)	0.89
Amiodarone use at randomization	2,364 (11.8)	128 (11.8)	0.99
Paroxysmal AF	5,098 (25.5)	268 (24.7)	0.19
History of coronary artery disease	6,618 (33.1)	405 (37.5)	**0.003**
History of carotid disease	1,121 (5.6)	69 (6.4)	0.27
History of CHF	11,461 (57.2)	663 (61.2)	**0.010**
History of diabetes	7,162 (35.8)	462 (42.7)	**<0.001**
History of dyslipidemia	10,422 (52.1)	636 (58.7)	**<0.001**
History of hypertension	18,730 (93.5)	1024 (94.6)	0.19
History of stroke or TIA	5,684 (28.4)	289 (26.7)	0.22
History of valvular heart disease	4,165 (20.8)	274 (25.3)	**<0.001**
Current smoker	1,453 (7.3)	99 (9.1)	**0.021**
VKA naive	8,259 (41.3)	404 (37.3)	**0.01**
CrCl <50 ml/min at randomization	3,898 (19.5)	176 (16.3)	**0.009**
CHA_2DS_2VASc score ≥4	14,191 (70.9)	728 (67.2)	**0.010**
Modified HAS-BLED Score ≥3	8,977 (44.8)	825 (76.2)	**<0.01**
Hepatic biomarkers			
AST, U/l	26.1 ± 9.0	39.1 ± 43.0	**<0.0001**
ALT, U/l	25.4 ± 12.0	43.7 ± 67.0	**<0.0001**
Alkaline phosphatase, U/l	91.3 ± 43.0	95.7 ± 43.0	0.08
Total bilirubin, mg/dl	0.53 ± 0.3	0.59 ± 0.35	**<0.0001**
Platelet count, n/μl	202.6 ± 55.8	195.1 ± 56.5	**<0.0001**
Hematocrit, %	42.2 ± 4.5	43.2 ± 4.8	**<0.0001**
Hemoglobin, g/dl	13.9 ± 1.5	14.2 ± 1.5	**<0.0001**
Endogenous FXa activity %	87.5 ± 24.0	91.2 ± 23.2	0.10

Values are mean ± SD or n (%). Scores on the CHA_2DS_2-VASc range from 0 to 9, with higher score indicating a greater risk of stroke; congestive heart failure, hypertension, 65 to 74 years of age, diabetes mellitus, vascular disease, and female sex are each assigned 1 point, and stroke or TIA or arterial thromboembolism, and ≥75 years of age are assigned 2 points. Scores on the HAS-BLED range from 0 to 9 with a higher score indicating a greater risk of major bleeding; hypertension, abnormal renal and liver function, stroke, bleeding history or predisposition, elderly, and history of drugs/alcohol are each assigned 1 point. Modified HAS-BLED incorporates standard score variables except for labile international normalized ratio, resulting in a maximum score of 8. *p = chi-square test (Kruskal-Wallis for continuous variables). **Bold** p values indicate statistical significance.

AF = atrial fibrillation; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65–74 years, sex category (female); CHF = congestive heart failure; CrCl = creatinine clearance; FXa = factor Xa; HAS-BLED = hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol; TIA = transient ischemic attack; VKA = vitamin K antagonist.

covariate. Safety analyses included all patients who received at least 1 dose of study drug. Because HDER is the approved edoxaban regimen in AF, clinical data on the LDER are presented in the Online Appendix. The proportional hazards assumption was satisfied.

RESULTS

Of 21,105 patients enrolled in ENGAGE AF-TIMI 48, 1,083 (5.1%) had a history of liver disease, equally distributed across treatment groups. Of these, 947 (87.0%) had a history of liver disease as determined by the site investigator, 136 (13.0%) had elevated liver enzymes (ALT/AST ≥2× ULN) at randomization, and 15 (1.4%) had both criteria. The distribution of characteristics of liver disease are shown in Figure 1.

BASELINE CHARACTERISTICS. Patients with liver disease were more often younger, obese, from eastern Europe and the Asia-Pacific region and had higher prevalence of coronary artery disease, congestive heart failure, diabetes mellitus, dyslipidemia, valvular heart disease, and current smoking than patients without liver disease (Table 1). Patients with liver disease had significantly higher baseline levels of AST, ALT, and total bilirubin. The baseline characteristics of patients with and without liver disease by randomized treatment arm (edoxaban vs. warfarin) were well matched ($p > 0.05$ for each) (Online Tables 2 and 3).

RISK OF SSEE AND BLEEDING. Among patients with liver disease, as compared with patients without liver disease, there was no significant difference in the adjusted risks of SSEE (1.55%/year vs. 1.82%/year; adjusted HR [HR_{adj}]: 0.90; 95% CI: 0.67 to 1.22; $p = 0.50$), ischemic SSEE (1.18%/year vs. 1.55%/year; HR_{adj}: 0.81; 95% CI: 0.58 to 1.14; $p = 0.23$), or hemorrhagic stroke (0.37%/year vs. 0.29%/year; HR_{adj}: 1.25; 95% CI: 0.67 to 2.34; $p = 0.48$) (Table 2). Similarly, in patients with liver disease, other prespecified endpoints including all-cause death, CV death, and myocardial infarction were not significantly different than in patients without liver disease.

The adjusted risks of ISTH major bleeding were significantly higher among patients with liver disease than among patients without liver disease (3.32%/year vs. 2.55%/year; HR_{adj}: 1.38; 95% CI: 1.10 to 1.74; $p = 0.006$) (Table 3). Similarly, liver disease was associated with higher adjusted risks of several other types of pre-defined bleeding events, including major or clinically relevant nonmajor bleeding. However, in patients with liver disease, the adjusted risks of intracranial hemorrhage and fatal bleeding were not significantly different than in patients without liver disease.

PK AND PD OF EDOXABAN AND WARFARIN IN PATIENTS WITH VERSUS WITHOUT LIVER DISEASE. The baseline endogenous FXa activity levels were not significantly different in patients with versus without

liver disease (Table 1). There were no significant differences in the peak and trough percentage inhibition in endogenous FXa activity at day 29 relative to baseline in patients with versus without liver disease across all edoxaban doses (Central Illustration, Online Table 4). Extrinsic FXa activity and edoxaban concentration on day 29 at trough were similar for the 2 groups with 1 exception (trough edoxaban concentration in patients randomized to LDER with liver disease were 4.2 ng/ml lower than in those without liver disease).

Among patients randomized to warfarin, there was no difference in time in the therapeutic range in patients with liver disease as compared with patients without liver disease (Online Table 5). A supratherapeutic INR of >3.0 occurred less frequently in the liver disease group versus without liver disease.

EFFICACY AND SAFETY IN PATIENTS WITH AND WITHOUT LIVER DISEASE. The annualized rate of SSEE for HDER versus warfarin was 1.57% versus 1.83% (HR: 0.86; 95% CI: 0.73 to 1.01) in patients without liver disease and 1.52% versus 1.38% (HR 1.11; 95% CI: 0.54 to 2.30) in patients with liver disease (p for interaction [p_{int}] = 0.47) (Figure 2, Central Illustration, Online Table 6). There were no significant interactions for the components of the primary efficacy endpoint (ischemic stroke, hemorrhagic stroke, systemic embolic event) ($p_{int} > 0.10$ for each). Consistently, there were no significant interactions for all-cause death in patients with and without liver disease ($p_{int} = 0.12$). Some composite endpoints that included CV death showed a significant interaction favoring warfarin in patients with a history of liver disease (Online Table 6).

The annualized rate of ISTH major bleeding for HDER versus warfarin was 2.81% versus 3.53% (HR: 0.80; 95% CI: 0.70 to 0.91) in patients without liver disease and 3.81% versus 4.32% (HR: 0.91; 95% CI: 0.56 to 1.47) in patients with liver disease ($p_{int} = 0.63$) (Figure 3, Online Table 7). No significant interactions were seen for fatal bleeding and clinically relevant nonmajor bleeding or major bleeding by presence of liver disease ($p_{int} = 0.69$ and 0.22, respectively) (Figure 3, Online Table 7).

The HRs for HDER, as compared with warfarin, for the primary net clinical outcome composite of SSEE, major bleeding, or death from any cause were 0.86 in patients without liver disease and 1.07 in patients with liver disease ($p_{int} = 0.26$) (Figure 3, Online Table 7). Neither of the interaction p values for the secondary and tertiary net clinical outcomes were significant.

TABLE 2 Thrombotic Events in Patients With Versus Without History of Liver Disease

	No Liver Disease (n = 20,022)		Liver Disease (n = 1,083)		Adjusted HRs (No Liver Disease vs. Liver Disease)*		
ITT Cohort, Overall Study Period	n	Event Rate (%/yr)	n	Event Rate (%/yr)	HR	95% CI	p Value
Primary endpoint							
Stroke or systemic embolic event	970	1.82	46	1.55	0.90	0.67–1.22	0.50
Ischemic stroke or systemic embolic event	827	1.55	35	1.18	0.81	0.58–1.14	0.23
Stroke	915	1.71	43	1.45	0.89	0.65–1.22	0.48
Hemorrhagic	158	0.29	11	0.37	1.25	0.67–2.34	0.48
Ischemic	772	1.44	32	1.07	0.79	0.55–1.14	0.20
Nondisabling and nonfatal	534	1.00	24	0.80	0.85	0.56–1.29	0.44
Disabling or fatal	406	0.75	19	0.63	0.89	0.56–1.43	0.64
Fatal	229	0.42	10	0.33	0.89	0.47–1.70	0.72
Systemic embolic event	63	0.12	4	0.13	1.25	0.45–3.47	0.67
Key secondary endpoints							
Stroke, systemic embolic event, or death from cardiovascular causes	2,255	4.21	100	3.36	0.88	0.72–1.08	0.22
Major adverse cardiac event	2,549	4.81	117	3.96	0.91	0.76–1.10	0.33
Stroke, systemic embolic event, or death	2,847	5.32	133	4.47	0.93	0.78–1.11	0.40
Other endpoints							
Death or intracranial hemorrhage	2,403	4.42	113	3.75	0.95	0.79–1.16	0.64
Death or disabling stroke	2,377	4.37	108	3.58	0.92	0.75–1.12	0.39
Death							
Any cause	2,246	4.08	103	3.39	0.94	0.77–1.15	0.56
Cardiovascular causes	1,599	2.91	69	2.27	0.89	0.70–1.14	0.37
Myocardial infarction	423	0.79	20	0.67	0.96	0.61–1.50	0.86

*Adjusted hazard ratio indicates adjustment for age, sex, body mass index, quartiles of creatinine, history of hypertension, history of dyslipidemia, history of diabetes, smoking, history of stroke or transient ischemic attack, history of heart failure, type of atrial fibrillation, race, region, history of increased risk of falling, history of neuropsychiatric disease, history of coronary artery disease, history of nonintracranial hemorrhage bleed, alcohol, and medication (antiplatelet agents or nonsteroidal anti-inflammatory drugs).

CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat.

Outcomes with lower-dose edoxaban regimen versus warfarin. The relative efficacy and safety outcomes of LDER versus warfarin in patients with and without liver disease were consistent with the results of the main trial, i.e., similar to warfarin for the prevention of SSEE and associated with lower rates of bleeding (all interaction p values were nonsignificant) (Online Tables 6 and 7).

HEPATIC SAFETY. The incidence of liver injury stratified by treatment group is summarized in Online Table 1. Drug-induced liver injury that met the criteria for Hy's law (20) was seen in 2 patients (0.03%) receiving HDER, 1 (0.01%) on LDER and 0 (0.0%) on warfarin. There were no significant differences in the rates of severe, moderate, mild, or minimal liver injury between both edoxaban regimens and warfarin. No cases of fulminant liver failure occurred in the trial.

TABLE 3 Bleeding Events in Patients With Versus Without History of Liver Disease

	No Liver Disease (n = 19,945)		Liver Disease (n = 1,081)		Adjusted HRs (No Liver Disease vs. Liver Disease)*		
Safety Cohort	n	Event Rate (%/yr)	n	Event Rate (%/yr)	HR	95% CI	p Value
Major bleeding	1,116	2.55	80	3.32	1.38	1.10–1.74	**0.006**
Fatal	107	0.24	5	0.20	0.96	0.39–2.39	0.93
Bleeding into a critical organ or area	364	0.82	24	0.98	1.19	0.78–1.81	0.41
Overt bleeding with blood loss ≥2 g/dl	773	1.76	58	2.39	1.51	1.15–1.98	**0.003**
Any intracranial bleeding	222	0.50	12	0.49	1.02	0.57–1.83	0.95
Fatal intracranial bleeding	75	0.17	3	0.12	0.81	0.25–2.61	0.72
Gastrointestinal bleeding	520	1.18	31	1.26	1.18	0.82–1.70	0.38
Upper gastrointestinal tract	319	0.72	20	0.81	1.22	0.77–1.92	0.40
Lower gastrointestinal tract	210	0.47	11	0.45	1.04	0.56–1.93	0.90
Bleeding in other location	390	0.88	39	1.60	1.94	1.39–2.72	**<0.001**
Life-threatening bleeding	211	0.47	13	0.53	1.12	0.64–1.97	0.69
Life-threatening bleeding or fatal	317	0.71	18	0.73	1.08	0.67–1.75	0.74
Major or clinically relevant nonmajor bleeding	4,172	10.50	278	13.12	1.24	1.09–1.40	**<0.001**
Any overt bleeding	5,152	13.53	326	16.10	1.22	1.09–1.37	**<0.001**
Net clinical outcomes							
Primary	3,821	7.38	212	7.45	1.10	0.96–1.27	0.16
Secondary	2,588	4.79	120	4.00	0.93	0.77–1.12	0.46
Tertiary	2,992	5.61	140	4.72	0.93	0.78–1.10	0.38

Bold p values indicate statistical significance. *Covariates adjusted are similar to Table 2.
Abbreviations as in Table 2.

DISCUSSION

This analysis represents the first report of PK, PD, clinical efficacy, and safety of edoxaban in patients with history of liver disease in a randomized trial of patients with AF. A history of liver disease, almost all of which was mild, was associated with a significantly increased risk of bleeding, and no difference in the risk of stroke compared with patients without liver disease. Second, the PK and PD of edoxaban were not modified by the presence of liver disease; consequently, the relative efficacy and safety of edoxaban (of both HDER and LDER) compared with warfarin for preventing SSEE or bleeding was maintained irrespective of liver disease status. Third, there were no significant differences in the rates of liver injury with either doses of edoxaban as compared with warfarin.

RISK OF STROKE AND BLEEDING IN LIVER DISEASE. Although patients with liver disease had a higher prevalence of risk factors for stroke (coronary artery disease, heart failure, diabetes, and valvular heart disease), we did not observe a higher adjusted risk of stroke in patients with liver disease. By contrast, several prior observational studies in the general population have found a higher adjusted risk of stroke in patients with liver disease (21,22). This has been attributed to a high prevalence of CV risk factors in patients with liver disease, particularly in those with nonalcoholic fatty liver disease, which is independently associated with increased CV risk (2,23).

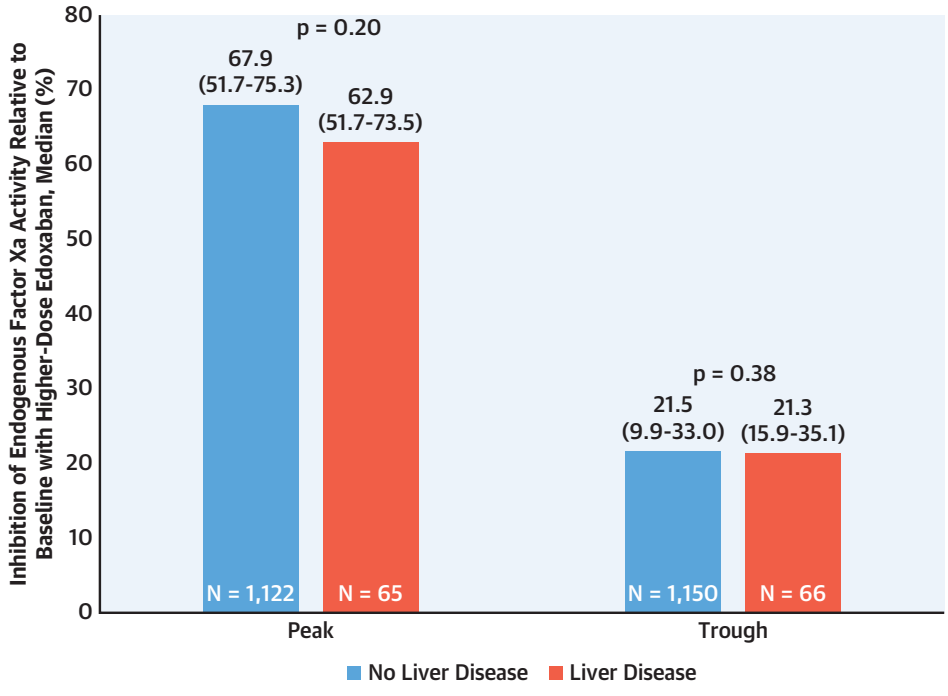
We found a higher incidence of a variety of types of bleeding in patients with liver disease versus those without liver disease. The association of liver disease with bleeding is well established. The pathophysiological mechanisms increasing bleeding in liver disease include: decreased production of coagulation factors, thrombocytopenia, and hyperfibrinolysis (5,24). As many patients with liver disease remain compensated and in the state of hemostatic balance except during episodes of decompensation or bleeding, this stability may have contributed to the absence of differences in the endogenous and extrinsic FXa activity we observed (25). Furthermore, alternate mechanisms of bleeding, such as platelet dysfunction or thrombocytopenia in patients with liver disease may have contributed to higher rates of bleeding (26).

PK AND PD OF EDOXABAN IN PATIENTS WITH LIVER DISEASE. We found no significant difference in antithrombotic effect of edoxaban measured by endogenous and extrinsic FXa activity in patients with and without liver disease. These results represent the PK and PD of edoxaban in patients with compensated liver disease and may change in patients with decompensated liver disease. In 1 small study, the PK and PD analysis of edoxaban showed similar peak edoxaban concentrations, prothrombin time, and partial thromboplastin time in patients with mild or moderate liver disease as compared with healthy controls (9,12). Although, our findings are consistent with the previous report, we also measured endogenous FXa activity, a more biologically significant pharmacodynamic measure of the anticoagulant effect of edoxaban (17) as compared with extrinsic FXa activity, prothrombin time, and partial thromboplastin time.

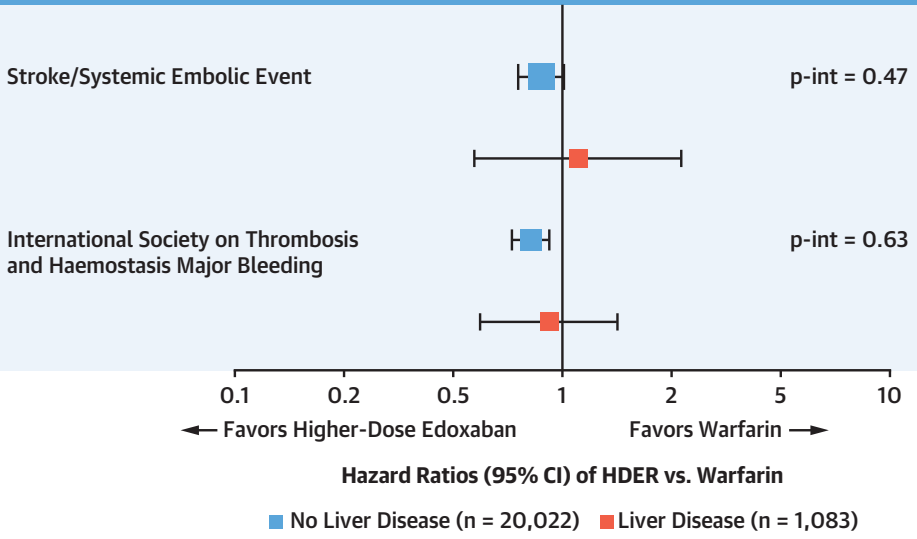
ORAL ANTICOAGULATION FOR STROKE PREVENTION IN AF AND LIVER DISEASE. Warfarin is usually the preferred oral anticoagulant agent in patients with AF and liver disease. However, no randomized clinical trial has evaluated the efficacy and safety of warfarin in patients with AF and liver disease, and most of the evidence on its use have been obtained from observational studies (5). These data suggest a reduced risk of stroke with warfarin compared with no anticoagulant therapy (27). Nonetheless, warfarin has several

CENTRAL ILLUSTRATION **Edoxaban in AF and History of Liver Disease in the ENGAGE-AF TIMI 48 Trial**

A Similar Factor Xa Inhibition With Edoxaban in Patients With and Without Liver Disease



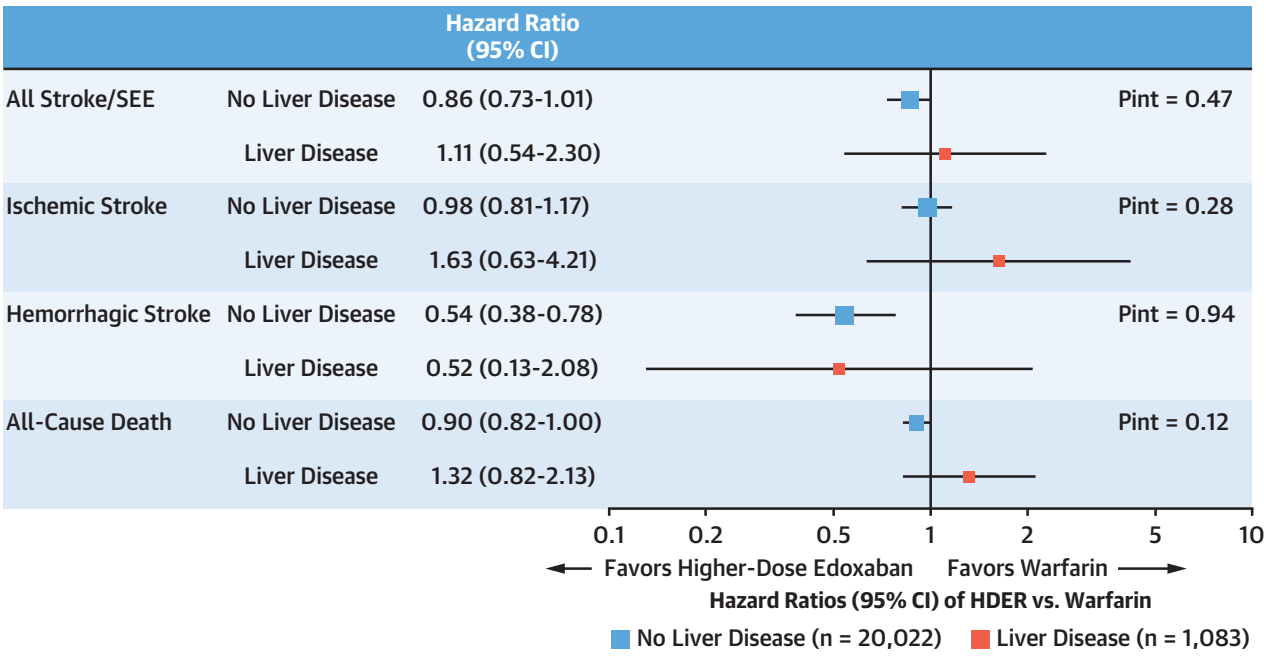
B Similar Effects of Edoxaban in Patients With and Without Liver Disease



Qamar, A. et al. J Am Coll Cardiol. 2019;74(2):179–89.

There were no significant differences in the peak and trough % inhibition in endogenous factor Xa activity relative to baseline with higher-dose edoxaban regimen in patients with versus without liver disease **(A)**. A history of liver disease did not alter the relative efficacy and safety of edoxaban compared to warfarin **(B)**. All values for inhibition in endogenous FXa activity are reported as median (interquartile range). AF = atrial fibrillation; ENGAGE AF-TIMI 48 = Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis In Myocardial Infarction 48; HDER = higher-dose edoxaban regimen; p-int = interaction p value.

FIGURE 2 Efficacy Outcomes of Higher-Dose Edoxaban Regimen Versus Warfarin



Forest plot is shown for efficacy outcomes in patients treated with higher-dose edoxaban versus those treated with warfarin, with or without history of liver disease. All efficacy endpoints are analyzed from the intention-to-treat study population. CI = confidence interval; HDER = higher-dose edoxaban regimen; Pint = interaction p value; SEE = systemic embolic event.

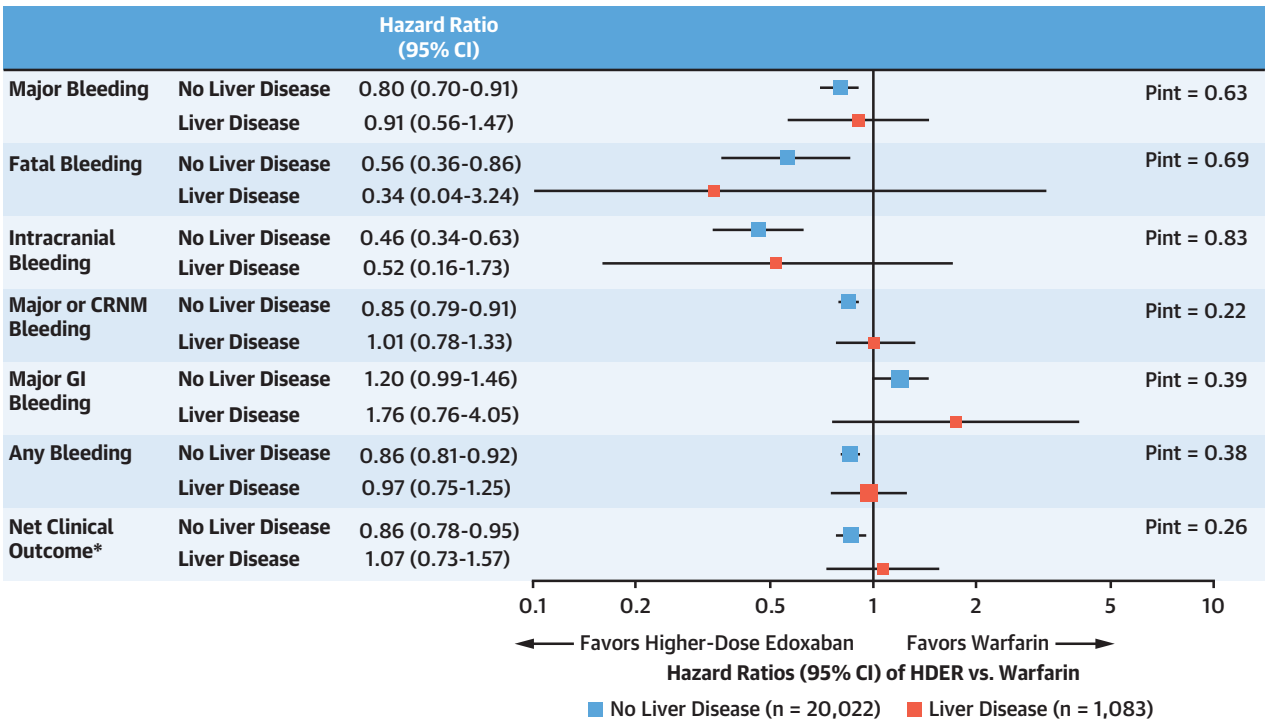
limitations compared with DOACs. In addition, patients with liver disease may have a prolonged INR at baseline, making it difficult to use warfarin (28). Randomized clinical trials of DOACs in patients with AF have mostly excluded patients with advanced liver disease. Hence, the evidence regarding the efficacy and safety of DOACs in patients with liver disease has been based largely on case reports, and small observational studies (29-32).

In this analysis, we found that patients with liver disease derive similar relative benefits of edoxaban compared with warfarin as patients without liver disease for the prevention of SSEE and bleeding. These findings are supported by consistent endogenous FXa activity, a marker of antithrombotic effect and of bleeding with edoxaban in patients with and without liver disease. We found significant interaction for CV death between patients with liver disease versus those without liver disease. Because there were very few CV deaths in patients with liver disease, this finding could be due to chance.

HEPATIC SAFETY OF DOACs. There have been concerns that DOACs may be associated with increased risk of hepatic injury, since ximelagatran, the first clinically available oral direct thrombin inhibitor was withdrawn from the European market in 2006 following reports of serious liver injury (33). We found no significant difference in the incidence of liver injury with edoxaban compared with warfarin. However, there are limited long-term safety data on the risk of liver injury with the currently approved DOACs. Moreover, a recent post-marketing safety review by Health Canada of the oral direct thrombin inhibitor dabigatran concluded that there may be a link between dabigatran and liver injury; an update to the safety information for dabigatran in Canada is planned (34).

The hepatic safety of apixaban and rivaroxaban have been closely monitored in randomized trials and several observational analyses, and their hepatic safety profiles have been reported to be comparable to edoxaban (7,8,35-37). However, the efficacy and safety of other DOACs in patients with history of liver disease or mild liver disease (Child Pugh A equivalent) in these trials have not been published. Prior, retrospective observational studies have reported at least similar efficacy in preventing thrombotic events and bleeding of all DOACs (including edoxaban) compared with warfarin in patients with advanced

FIGURE 3 Safety Outcomes of Higher-Dose Edoxaban Regimen Versus Warfarin



Forest plots are shown for safety outcomes in patients treated with higher-dose edoxaban versus those treated with warfarin, with or without a history of liver disease. All bleeding endpoints are analyzed from the on-treatment study population, which began with first dose of study treatment through last dose plus 3 days. *Net clinical outcome = death from any cause, stroke, systemic embolic event, or major bleeding. CRNM = clinically relevant nonmajor bleeding; GI = gastrointestinal; other abbreviations as in Figure 2.

liver disease and AF or venous thromboembolism (29-32,38). Furthermore, an observational study showed comparable efficacy in lowering risk of ischemic stroke/systemic embolism and lower risk of bleeding with low-dose DOACs compared with warfarin (38). Nonetheless, the findings from these observational studies should be interpreted with caution because of the vulnerability to residual confounding, bias, and low power. Because off-label use of low-dose DOACs are less effective to prevent thrombotic events, their use, in general, should be discouraged.

STUDY LIMITATIONS. First, this study represents an exploratory subgroup analysis with limited power due to a small number of events in the liver disease group that resulted in wide CIs and should therefore be considered hypothesis-generating rather than definitive evidence. Nonetheless, this analysis is the largest (n = 1,083, 5.1% of the patients enrolled) and longest (2.8 years median follow-up) evaluation of patients with AF and liver disease receiving a DOAC. Second, patients were identified as having a history of liver disease at baseline by site investigators, and no formal evaluation was required; thus, some misclassification may have occurred. Therefore, future trials should consider a more objective prespecified definition of liver disease (e.g., imaging and biomarker). Third, the trial did not include patients with active or advanced chronic liver disease; thus, our findings are applicable to patients with mild liver disease, and the efficacy and safety of edoxaban compared with warfarin in patients with moderate or severe liver disease cannot be determined from this analysis. Fourth, the current regulatory guidance on the use of DOACs in patients with liver disease requires assessment of baseline liver disease severity with Child-Pugh classification, which includes INR in addition to other clinical parameters, but we could not estimate the Child-Pugh score in this analysis

because of the high rate (73%) of use of vitamin K antagonists before enrollment. However, because ENGAGE AF-TIMI 48 excluded patients with active liver disease, or those with chronic severe derangement of liver function, INR, and platelet count, the severity of liver disease of patients in this analysis is most comparable with Child-Pugh class A. In addition, patients with versus without liver disease had significant differences in baseline characteristics; although we included them in the multivariable analysis, some unmeasured confounders may still influence the results. Finally, we did not correct for multiple comparisons, thereby increasing the risk of type I error.

CONCLUSIONS

In a large randomized clinical trial of patients with AF receiving oral anticoagulation, the history of mild liver disease is associated with a higher risk of bleeding without change in relative efficacy of edoxaban compared with warfarin for the reduction of SSEE and bleeding. There was no significant difference in hepatic adverse events between edoxaban and warfarin. In the setting of high risk of bleeding in patients with liver disease, edoxaban should be preferred over warfarin for the prevention of stroke and bleeding in patients with AF and history of liver disease.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: A history of mild liver disease is associated with a higher risk of bleeding during anticoagulation therapy but does not change the relative efficacy and safety of edoxaban compared with warfarin in patients with atrial fibrillation. There is no significant difference in hepatic adverse events between the 2 treatments.

TRANSLATIONAL OUTLOOK: Patients with advanced liver disease are at high risk of thrombotic and bleeding events, and large prospective trials are needed to evaluate the efficacy and safety of target-specific oral anticoagulant agents in this vulnerable population.

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KEY WORDS atrial fibrillation, bleeding, liver disease, stroke

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