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Dose Reduction of Edoxaban in Patients 80 Years and Older With Atrial Fibrillation

Post Hoc Analysis of the ENGAGE AF-TIMI 48 Randomized Clinical Trial

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IMPORTANCE In older patients with atrial fibrillation who take anticoagulants for stroke prevention, bleeding is increased compared with younger patients, thus, clinicians frequently prescribe lower than recommended doses in older patients despite limited randomized data.

OBJECTIVE To evaluate ischemic and bleeding outcomes in patients 80 years and older with atrial fibrillation receiving edoxaban, 60 mg vs 30 mg, and edoxaban, 30 mg vs warfarin.

DESIGN, SETTING, AND PARTICIPANTS The ENGAGE AF-TIMI 48 trial (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48) was a parallel-design, double-blind, global clinical trial that randomized patients with atrial fibrillation to either one of 2 edoxaban dosing regimens or warfarin. This secondary analysis focused on patients 80 years or older without dose-reduction criteria receiving edoxaban, 60 mg vs 30 mg, as well as patients with or without dose-reduction criteria receiving edoxaban, 30 mg, vs warfarin. Study data were analyzed between October 2022 and December 2023.

INTERVENTIONS Oral edoxaban, 30 mg once daily; edoxaban, 60 mg once daily; or warfarin.

MAIN OUTCOMES AND MEASURES Primary net clinical outcome of death, stroke or systemic embolism, and major bleeding and each individual component.

RESULTS The current analysis included 2966 patients 80 years and older (mean [SD] age, 83 [2.7] years; 1671 male [56%]). Among 1138 patients 80 years and older without dose-reduction criteria, those receiving edoxaban, 60 mg vs 30 mg, had more major bleeding events (hazard ratio [HR], 1.57; 95% CI, 1.04-2.38; $P = .03$), particularly gastrointestinal hemorrhage (HR, 2.24; 95% CI, 1.29-3.90; $P = .004$), with no significant difference in efficacy end points. Findings were supported by analyses of endogenous factor Xa inhibition, a marker of anticoagulant effect, which was comparable between younger patients receiving edoxaban, 60 mg, and older patients receiving edoxaban, 30 mg. In 2406 patients 80 years and older with or without dose-reduction criteria, patients receiving edoxaban, 30 mg, vs warfarin had lower rates of the primary net clinical outcome (HR, 0.78; 95% CI, 0.68-0.91; $P = .001$), major bleeding (HR, 0.59; 95% CI, 0.45-0.77; $P < .001$), and death (HR, 0.83; 95% CI, 0.70-1.00; $P = .046$), whereas rates of stroke or systemic embolism were comparable.

CONCLUSIONS AND RELEVANCE In this post hoc analysis of the ENGAGE AF-TIMI 48 randomized clinical trial, in patients 80 years and older with atrial fibrillation, major bleeding events were lower in patients randomized to receive edoxaban, 30 mg per day, compared with either edoxaban, 60 mg per day (in patients without dose-reduction criteria), or warfarin (irrespective of dose-reduction status), without an offsetting increase in ischemic events. These data support the concept that lower-dose anticoagulants, such as edoxaban, 30 mg, may be considered in older patients with atrial fibrillation even in the absence of dose-reduction criteria.

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Visual Abstract

Supplemental content

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Older individuals with atrial fibrillation (AF) who are taking oral anticoagulants are at high risk for bleeding for numerous reasons,[1,2] including chronic kidney disease,[3] frailty,[4] polypharmacy,[4] multimorbidity,[5] and risk of falls,[6] and the risk increases with a greater number of high-risk features.[7] As bleeding risk increases with age, clinicians often use lower than recommended doses of anticoagulants or even avoid anticoagulation altogether, placing older individuals at higher risk of ischemic events.[8-11] Notably, although older patients have high rates of AF and widespread use of alternative doses in clinical practice,[8-10] there are limited randomized data comparing the efficacy and safety of lower doses of anticoagulants in this patient population to inform decision-making.

In the ENGAGE AF-TIMI 48 trial (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48), 2 dosing regimens of edoxaban were compared with warfarin in patients with AF. A higher-dose edoxaban regimen (HDER) of 60 mg once daily, reduced to 30 mg per protocol in patients with dose-reduction criteria, proved to be an effective and safe therapy.[12] However, with the lower-dose edoxaban regimen (LDER) of 30 mg once daily (reduced to 15 mg in patients with dose-reduction criteria), the rate of ischemic stroke was 41% higher than that with warfarin. Because of this finding, the LDER was not approved for clinical use, despite providing significant reductions compared with warfarin in all-cause and cardiovascular death, major bleeding events (including a significant 33% reduction in major gastrointestinal bleeding), and the prespecified primary net clinical outcome of stroke or systemic embolism, major bleeding, and death. Nonetheless, clinical interest in lower-dose anticoagulation regimens remains, and data exist suggesting that lower dosing regimens of edoxaban may benefit selected patients at high bleeding risk.[13,14] Of note, an even lower dose of edoxaban, 15 mg daily, in all patients was compared with placebo in the ELDERCARE-AF (Edoxaban Low-Dose for Elder Care Atrial Fibrillation Patients) trial[14] of Japanese patients with AF who were 80 years and older and deemed ineligible for standard anticoagulation. Results showed that edoxaban, 15 mg daily, significantly reduced the risk of stroke or systemic embolism by 66% vs placebo.[14]

Three prespecified analyses of the ENGAGE AF-TIMI 48 trial established the rationale for the current study. First, although ischemic events, bleeding, and death increase markedly with older age, the treatment effect of HDER was even more favorable in older than in younger patients in ENGAGE AF-TIMI 48.[15] Second, a pharmacokinetic/pharmacodynamic analysis showed that older adults, as compared with younger patients, had lower levels of endogenous factor Xa (FXa) activity at baseline (without anticoagulation), indicating increased risk of bleeding. They also exhibited an exaggerated response to an oral FXa inhibitor.[16] Finally, patients randomized to LDER (vs HDER) were significantly less likely to experience the prespecified primary net clinical outcome of stroke or systemic embolic event (SEE), major bleeding, or death from any cause.[13] This result was driven by fewer major bleeding events at the cost of more ischemic events, suggesting either dosing regimens may be appropriate depending on a patient's risk profile and personal preferences.[13] In aggregate, a strategy based on pharmacokinetic and pharmacodynamic data and their relationship to clinical outcomes could represent a rational approach for dose selection in the older patient population.[17]

In this post hoc analysis of patients 80 years and older with AF from the ENGAGE AF-TIMI 48 trial, we studied the outcomes of patients randomized to edoxaban, 60 mg vs 30 mg (in patients without dose-reduction criteria), and edoxaban, 30 mg (irrespective of dose-reduction criteria), vs warfarin.

Key Points

Question Do patients 80 years and older with atrial fibrillation who are at high risk of ischemic and bleeding events benefit from lower-dose anticoagulants, even in the absence of prespecified dose-reduction criteria?

Findings In this post hoc analysis of 2966 patients with atrial fibrillation 80 years and older, major bleeding events were lower among those randomized to edoxaban, 30 mg per day, compared with either edoxaban, 60 mg per day (in patients without dose-reduction criteria), or warfarin (irrespective of dose-reduction criteria), without an offsetting increase in ischemic events.

Meaning Lower-dose anticoagulants, such as edoxaban, 30 mg once daily, may be considered in patients 80 years and older with atrial fibrillation, regardless of the presence of dose-reduction criteria.

Methods

Study Design

The design and results of ENGAGE AF-TIMI 48 have been reported previously (Supplement 1).[12,18] In brief, ENGAGE AF-TIMI 48 was a phase 3, multicenter, 3-group, double-blind, double-dummy, randomized clinical trial testing the efficacy and safety of 2 dose regimens of edoxaban in 21 105 patients with AF. Patients were randomized 1:1:1 to receive HDER (60/30 mg), LDER (30/15 mg), or warfarin once daily. The edoxaban dose was reduced in both edoxaban arms by 50% (ie, HDER: from 60 to 30 mg; LDER: from 30 to 15 mg) in patients with creatinine clearance of 50 mL/min or less, body weight of 60 kg or less, or taking strong P-glycoprotein (permeability glycoprotein) inhibitors at the time of randomization or during the treatment phase. The study protocol was approved by institutional review boards at each participating center. All patients provided written informed consent. This study is reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Study Population

Adults with documented AF within the prior year and $CHADS_2$ score of 2 or greater ($CHADS_2$ indicates congestive heart failure, hypertension, age ≥75 years, diabetes, prior stroke or transient ischemic attack [2 points]), in whom anticoagulation was planned for prevention of thromboembolism, were eligible for

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participation. Participants self-identified with the following races and ethnicities: African American or Black, Asian, White, and other, which included American Indian or Alaska Native and Native Hawaiian or Other Pacific Islander. Key exclusion criteria were estimated creatinine clearance less than 30 mL/min, moderate or severe mitral stenosis, mechanical heart valve, high risk of bleeding (eg, history of overt gastrointestinal bleeding, hemorrhagic disorder, or recent major surgery), use of dual antiplatelet therapy, and AF due to a reversible disorder. There was no upper age limit for participation.

Study End Points

The primary efficacy end point of the trial was any stroke or SEE. The principal safety end point was major bleeding, as defined by the International Society on Thrombosis and Hemostasis.[19] Secondary end points included ischemic stroke, intracranial hemorrhage, all-cause death, and the predefined primary net clinical outcome of stroke, SEE, major bleeding, or death from any cause. Exploratory end points included major gastrointestinal bleeding, secondary net clinical outcome (disabling stroke, life-threatening bleed, or death), and tertiary net clinical outcome (stroke, SEE, life-threatening bleed, or death). All end points were adjudicated by an independent adjudication committee blinded to randomized treatment assignment.

Edoxaban Pharmacokinetic and Pharmacodynamic Analyses

Edoxaban plasma concentration and inhibition of endogenous FXa activity were assessed as previously described.[20] Blood samples for edoxaban concentrations at trough were collected 4 weeks after randomization, before the daily dose. Blood samples for endogenous FXa activity, a direct measure of the functional activity of endogenous FX in plasma,[16,21] were collected at baseline and 4 weeks after randomization, before the dose. This result is reported as a percentage of normal control samples. The pharmacokinetic and pharmacodynamic comparisons of interest were between edoxaban, 60 mg vs 30 mg, in patients without dose-reduction criteria, further grouped by age younger than 80 years and 80 years and older.

Statistical Analysis

The current analyses focused on patients 80 years and older, including patients without dose-reduction criteria randomized to edoxaban, 30 mg (LDER); edoxaban, 60 mg (HDER); or warfarin and patients with dose-reduction criteria randomized to edoxaban, 30 mg (HDER), or warfarin. The principal comparison of interest was between patients 80 years and older without dose-reduction criteria receiving edoxaban, 60 mg vs 30 mg. Patients who received edoxaban, 15 mg, were excluded. Baseline characteristics are reported as median with IQR for continuous variables and total number with percentage for categorical variables. Continuous variables were compared using Wilcoxon rank-sum test, and categorical variables were compared with χ^2 test.

The randomized comparisons between edoxaban, 60 mg vs 30 mg, in patients without dose-reduction criteria and between edoxaban, 30 mg, vs warfarin in overall patients were prespecified in the ENGAGE AF-TIMI 48 statistical analysis plan.[12] For the current post hoc analysis, the subgroup of participants who were 80 years and older was chosen before statistical analyses for this study to reflect a sample of older patients based on the population from previous randomized trials[14,22] and because an age of 80 years or older is 1 of 3 dose-reduction criteria for apixaban in AF.[23,24] For comparisons of treatment effect, we computed a time-to-first-event analysis using a Cox proportional hazards model. The proportional hazards assumption was confirmed based on scaled Schoenfeld residuals. Comparisons were adjusted for treatment group and randomization stratification criteria, namely dose-reduction status and $CHADS_2$ risk score greater than 3.

All analyses were conducted using SAS, version 9.4 (SAS Institute), or higher and R, version 4.1.2 (R Project for Statistical Computing). A 2-sided P value <.05 was considered statistically significant. There was no adjustment for multiple comparisons. Study data were analyzed between October 2022 and December 2023.

Results

Patient Characteristics

The ENGAGE AF-TIMI 48 main trial enrolled 21 105 participants in 46 countries from November 19, 2008, to November 22, 2010. The current analysis included 2966 patients 80 years and older (mean [SD] age, 83 [2.7] years; 1295 female [44%]; 1671 male [56%]), including 1700 patients without dose-reduction criteria randomized to edoxaban, 30 mg (LDER; n = 578); edoxaban, 60 mg (HDER; n = 560); or warfarin (n = 562), and 1266 patients with dose-reduction criteria randomized to edoxaban, 30 mg (HDER with dose reduction; n = 623), or warfarin (n = 643) (**Figure 1** and eFigure 1 in Supplement 2). Baseline characteristics of the patients were well-matched, both overall and within the subgroup without dose-reduction criteria (**Table 1**). Patients identified with the following races and ethnicities: 26 African American or Black (1%), 237 Asian (8%), 2567 White (87%), or 136 other (5%).

Overall, the median age was 82 years, most patients were male, and a minority had paroxysmal AF. Slightly more than one-half of patients met criteria for dose reduction at randomization, primarily due to kidney impairment. Patients who did not meet dose-reduction criteria were younger, had a lower CHA_2DS_2-VASc score (CHA_2DS_2-VASc indicates congestive heart failure, hypertension, age 65-74 years [1 point] or ≥75 years [2 points], diabetes, prior stroke or transient ischemic attack or thromboembolism [2 points], vascular disease, and sex category [female]), and had fewer comorbidities (Table 1 and eTable 1 in Supplement 2).

Clinical Outcomes With Edoxaban, 60 mg vs 30 mg, in Patients 80 Years and Older Without Dose-Reduction Criteria

Among patients 80 years and older in the ENGAGE AF-TIMI 48 trial, 1891 (52.7%) met the criteria for dose reduction at randomization, mainly due to creatinine clearance of 50 mg/dL or less (1818 [96.1%]) and weight of 60 kg or less (614 [32.5%]; of note: patients could meet more than 1 criterion). In an analysis comparing edoxaban, 60 mg vs 30 mg, in patients 80 years and older without dose-reduction criteria, incidences of either

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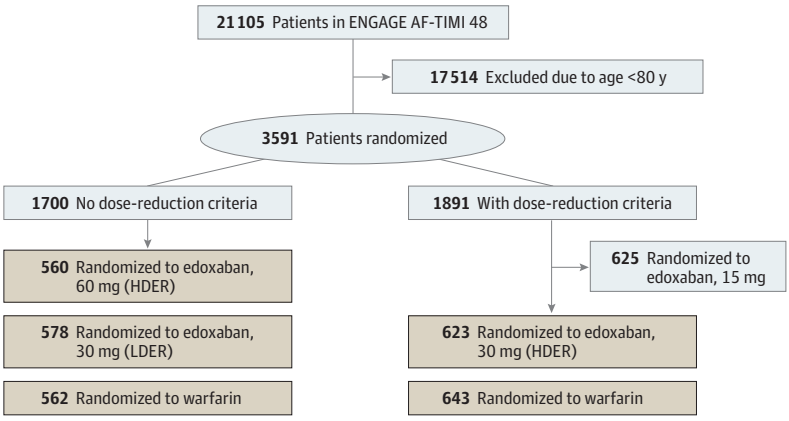
Figure 1. Patient Flowchart



A total of 2966 patients 80 years and older were randomized to edoxaban, 30 mg once daily; edoxaban, 60 mg once daily; or warfarin and included in this analysis. Comparisons between edoxaban, 30 mg (n = 1201), vs warfarin (n = 1205) included all patients randomized to the respective dosing arm regardless of the presence of dose-reduction criteria. Comparisons between edoxaban, 30 mg (n = 578), vs edoxaban, 60 mg (n = 560), vs warfarin (n = 562) included patients without dose-reduction criteria. The edoxaban dose was reduced by 50% in patients meeting 1 or more of the following dose reduction criteria: creatinine clearance of 50 mL/min or less, body weight of 60 kg or less, or use of concomitant strong P-glycoprotein (permeability glycoprotein) inhibitors. ENGAGE AF-TIMI 48 indicates Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48; HDER, higher-dose edoxaban regimen (60/30 mg); LDER, lower-dose edoxaban regimen (30/15 mg).

net clinical outcomes or stroke/SEE were not significantly different between the randomized arms (**Table 2** and **Figure 2**). Rates of major bleeding were higher with edoxaban, 60 mg, compared with edoxaban, 30 mg (hazard ratio [HR], 1.57; 95% CI, 1.04-2.38; P = .03). Moreover, rates of major gastrointestinal bleeding were greater with edoxaban, 60 mg, than edoxaban, 30 mg (HR, 2.24; 95% CI, 1.29-3.90; P = .004) (**Figure 3**A). There were no significant differences between edoxaban, 60 mg, and edoxaban, 30 mg, for the end points of all-cause death or ischemic stroke.

Edoxaban Pharmacokinetic and Pharmacodynamic Analyses

Edoxaban concentration and inhibition of FXa at trough increased with age for any given dose. Patients 80 years and older who received edoxaban, 30 mg, regardless of dose-reduction criteria, had a median trough concentration that approximated that of patients younger than 80 years who received edoxaban, 60 mg. The median (IQR) trough concentrations in patients 80 years and older who received edoxaban, 30 mg, were 30.5 (17.7-46.6) ng/mL if dose-reduction factors were present and 25.4 (15.4-38.3) ng/mL if dose-reduction factors were absent, compared with 34.6 (18.8-60.8) ng/mL in patients younger than 80 years who received edoxaban, 60 mg (eTable 2 in Supplement 2). Conversely, in patients 80 years and older receiving edoxaban, 60 mg, the median (IQR) trough edoxaban concentration was 35% higher than in patients younger than 80 years receiving edoxaban, 60 mg (46.6 [29.5-72.0] ng/mL vs 34.6 [18.8-60.8] ng/mL; P < .001).

Moreover, older patients exhibited more intense inhibition of endogenous FXa activity for any given dose of edoxaban, indicating a greater anticoagulant effect. Even in the absence of dose-reduction criteria, edoxaban, 30 mg, in older patients achieved similar a degree of endogenous FXa inhibition as edoxaban, 60 mg, in younger patients. For example, 82-year-old patients receiving edoxaban, 30 mg, and 67-year-old patients receiving edoxaban, 60 mg, achieved the same predicted trough FXa activity of 71% (Figure 3B).

Clinical Outcomes With Edoxaban, 30 mg, vs Warfarin in Patients 80 Years and Older Irrespective of Dose-Reduction Criteria

In 2406 patients 80 years and older, irrespective of dose-reduction criteria, the net clinical outcome was 22% lower (HR, 0.78; 95% CI, 0.68-0.91; P = .001) with edoxaban, 30 mg, compared with warfarin (eFigure 2 in Supplement 2). Rates of stroke or SEE were similar between groups (HR, 0.93; 95% CI, 0.69-1.27; P = .66), but major bleeding events overall were lower with edoxaban, 30 mg (HR, 0.59; 95% CI, 0.45-0.77; P < .001); the curves separated early and continued to diverge indicating a sustained and even more pronounced reduction in bleeding over time. Rates of major gastrointestinal bleeding did not differ between treatment arms. All-cause death was 17% lower (HR, 0.83; 95% CI, 0.70-1.00; P = .046) with edoxaban, 30 mg, vs warfarin in patients older than 80 years. Although rates of ischemic stroke were not different between treatments, intracranial hemorrhage was 51% lower (HR, 0.49; 95% CI, 0.28-0.87; P = .02) in patients randomized to edoxaban, 30 mg. There was no significant effect modification by dose-reduction criteria for any of the end points (P for interaction >.05 for each), which suggests that the efficacy and safety profile of edoxaban, 30 mg, vs warfarin was consistent across dose-reduction strata (eFigure 3 in Supplement 2).

Discussion

The unique 3-group design of the ENGAGE AF-TIMI 48 trial enabled comparisons between patients randomized to edoxaban, 30 mg, vs edoxaban, 60 mg, vs warfarin. The current

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Table 1. Baseline Characteristics of Patients 80 Years and Older by Randomized Group

Characteristic	Overall, No. (%)		Without dose-reduction criteria, No. (%)		
	Edoxaban 30 mg (n = 1201)	Warfarin (n = 1205)	Edoxaban, 30 mg (n = 578)	Edoxaban, 60 mg (n = 560)	Warfarin (n = 562)
Age, median (IQR), y	82 (81-85)	82 (81-84)	82 (81-84)	82 (80.5-84)	82 (80-84)
Sex					
Female	550 (45.8)	544 (45.1)	210 (36.3)	201 (35.9)	186 (33.1)
Male	651 (54.2)	661 (54.9)	368 (63.7)	359 (64.1)	376 (66.9)
Race					
African American or Black	12 (1.0)	8 (0.7)	3 (0.5)	6 (1.1)	2 (0.4)
Asian	106 (8.8)	110 (9.1)	14 (2.4)	21 (3.8)	16 (2.8)
White	1024 (85.3)	1025 (85.1)	548 (94.8)	518 (92.5)	521 (92.7)
Other[a]	59 (4.9)	62 (5.1)	13 (2.2)	15 (2.7)	23 (4.1)
Region					
North America	402 (33.5)	437 (36.3)	213 (36.9)	218 (38.9)	225 (40)
Latin America	198 (16.5)	189 (15.7)	85 (14.7)	76 (13.6)	83 (14.8)
Western Europe	208 (17.3)	231 (19.2)	109 (18.9)	122 (21.8)	124 (22.1)
Eastern Europe	251 (20.9)	216 (17.9)	139 (24.0)	109 (19.5)	103 (18.3)
Asia-Pacific and South Africa	142 (11.8)	132 (11)	32 (5.5)	35 (6.3)	27 (4.8)
Paroxysmal atrial fibrillation	325 (27.1)	304 (25.2)	153 (26.5)	121 (21.6)	133 (23.7)
Qualifying risk factor					
Age ≥75 y	1201 (100)	1205 (100)	578 (100)	560 (100)	562 (100)
Prior stroke or transient ischemic attack	297 (24.7)	332 (27.6)	131 (22.7)	142 (25.4)	147 (26.2)
Congestive heart failure	567 (47.2)	539 (44.7)	254 (43.9)	233 (41.6)	233 (41.5)
Diabetes mellitus	298 (24.8)	310 (25.7)	153 (26.5)	165 (29.5)	170 (30.2)
Hypertension requiring treatment	1095 (91.2)	1130 (93.8)	531 (91.9)	519 (92.7)	529 (94.1)
Vascular disease	285 (23.7)	295 (24.5)	137 (23.7)	115 (20.5)	128 (22.8)
$CHADS_2$ score 4-6[b]	374 (31.1)	410 (34)	167 (28.9)	178 (31.8)	190 (33.8)
CHA_2DS_2-VASc score 5-9[c]	715 (59.5)	735 (61.0)	322 (55.7)	321 (57.3)	324 (57.7)
HAS-BLED score ≥3[d]	691 (57.5)	716 (59.4)	317 (54.8)	316 (56.4)	324 (57.7)
Prior nonintracranial bleeding	169 (14.1)	170 (14.1)	83 (14.4)	64 (11.4)	85 (15.1)
Prior gastrointestinal bleeding	68 (5.7)	73 (6.1)	29 (5.0)	25 (4.5)	39 (6.9)
Dose reduction at randomization	623 (51.9)	643 (53.4)	0	0	0
Creatinine clearance ≤50 mL/min	606 (50.5)	616 (51.1)	82 (14.2)	91 (16.3)	70 (12.5)
Weight ≤60 kg	201 (16.7)	208 (17.3)	0	2 (0.4)	0
Use of verapamil, quinidine, or dronedarone	31 (2.6)	37 (3.1)	1 (0.2)	2 (0.4)	2 (0.4)
Time in therapeutic range, median (IQR), %	NA	69.5 (57.8-78.5)	NA	NA	71.9 (60.5-79)

Abbreviations: $CHADS_2$, congestive heart failure, hypertension, age ≥75 years, diabetes, prior stroke or transient ischemic attack (2 points); CHA_2DS_2-VASc, congestive heart failure, hypertension, age 65-74 years (1 point) or ≥75 years (2 points), diabetes, prior stroke or transient ischemic attack or thromboembolism (2 points), vascular disease, and sex category (female); HAS-BLED, hypertension, kidney disease, liver disease, prior stroke, history of bleeding, age >65 years, use of aspirin and other antiplatelets, and alcohol use disorder, excluding labile international normalized ratio; NA, not applicable.

[a] Other race includes American Indian or Alaska Native and Native Hawaiian or Other Pacific Islander.

[b] The $CHADS_2$ score ranges from 0 to 6.

[c] The CHA_2DS_2-VASc score ranges from 0 to 9, with higher scores indicating an increased risk of stroke.

[d] The HAS-BLED score ranges from 0 to 9, with higher scores indicating an increased risk of major bleeding.

analysis focusing on patients 80 years and older demonstrates that, in patients 80 years and older without dose-reduction criteria, reduction of the edoxaban dose from 60 mg to 30 mg was associated with lower rates of major gastrointestinal bleeding, observed with 60 mg in this age group, without an offsetting increase in ischemic stroke. These findings were supported by pharmacokinetic and pharmacodynamic analyses demonstrating that patients 80 years and older achieved higher edoxaban concentrations and inhibition of endogenous FXa, indicating that the same dose of edoxaban had a more pronounced anticoagulant effect in older patients than in younger patients. Additionally, patients randomized to and receiving edoxaban, 30 mg, irrespective of dose-reduction status, experienced lower rates of net outcomes, major bleeding, and all-cause death vs warfarin with similar rates of stroke or systemic embolism.

In the ENGAGE AF-TIMI 48 trial, the daily dose of edoxaban ranged from 15 mg to 60 mg, and dose reduction was performed with the goal of avoiding high levels of drug exposure in vulnerable patient subgroups.[20] However, residual bleeding risk in older patients and a high predicted plasma level of drug exposure may represent an opportunity for targeted dose adjustment, even in the absence of prespecified dose-reduction criteria based on kidney function, weight, and use of strong P-glycoprotein inhibitor.[17] Specific pharmacodynamic assessments of inhibition of endogenous FXa activity with edoxaban,[16] a biologically more relevant marker of the anticoagulant effect of a factor Xa inhibitor than drug concentrations or anti-FXa activity, demonstrated that compared with younger adults, older adults had lower levels of endogenous FXa activity at baseline without an anticoagulant (hence higher risk of bleeding at baseline) and a greater degree of inhibition of endogenous FXa after receiving the same dose of edoxaban as younger patients. These findings were consistent with the clinical outcomes reported in the present analysis: patients 80 years and older with no dose-reduction criteria receiving edoxaban, 60 mg, had a 57% higher rate of major bleeding and a 124% higher rate of major gastrointestinal bleeding

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Table 2. Effect of Edoxaban vs Warfarin in Patients 80 Years and Older Without Dose-Reduction Criteria

Outcome[a]	Edoxaban, 60 mg (n = 560)	Edoxaban, 30 mg (n = 578)	Warfarin (n = 562)	HR (95% CI)		
				Edoxaban, 60 mg vs 30 mg	Edoxaban, 30 mg vs warfarin	Edoxaban, 60 mg vs warfarin
Stroke or systemic embolism	28 (1.93)	34 (2.26)	32 (2.20)	0.83 (0.50-1.36)	1.05 (0.65-1.70)	0.89 (0.53-1.47)
Major bleeding	54 (4.84)	39 (3.08)	70 (6.02)	1.57 (1.04-2.38)[b]	0.52 (0.35-0.77)[b]	0.81 (0.57-1.15)
Primary net clinical outcome[c]	147 (10.65)	137 (9.47)	163 (11.87)	1.11 (0.88-1.40)	0.81 (0.65-1.02)	0.90 (0.72-1.12)
All-cause death	81 (5.35)	84 (5.37)	93 (6.16)	0.98 (0.72-1.34)	0.89 (0.66-1.19)	0.86 (0.64-1.16)
Ischemic stroke	22 (1.51)	26 (1.72)	22 (1.50)	0.84 (0.48-1.49)	1.19 (0.67-2.10)	1.02 (0.57-1.85)
Intracranial hemorrhage	5 (0.44)	9 (0.70)	20 (1.66)	0.61 (0.20-1.83)	0.42 (0.19-0.93)[b]	0.26 (0.10-0.69)[b]
Major gastrointestinal bleeding	37 (3.28)	19 (1.49)	21 (1.76)	2.24 (1.29-3.90)[b]	0.87 (0.47-1.62)	1.91 (1.12-3.27)[b]
Secondary net clinical outcome[d]	94 (6.38)	90 (5.89)	110 (7.48)	1.07 (0.80-1.43)	0.80 (0.60-1.06)	0.85 (0.64-1.12)
Tertiary net clinical outcome[e]	107 (7.38)	104 (6.90)	121 (8.34)	1.05 (0.80-1.38)	0.84 (0.65-1.10)	0.89 (0.68-1.15)

Abbreviations: $CHADS_2$, congestive heart failure, hypertension, age ≥75 years, diabetes, prior stroke or transient ischemic attack (2 points); HR, hazard ratio.

[a] Outcomes are reported as total number of patients affected and annualized incidence. Models were adjusted for $CHADS_2$ score greater than 3.

[b] $P < .05$

[c] The primary net clinical outcome is a composite of stroke, systemic embolic event, major bleeding, or death from any cause.

[d] The secondary net clinical outcome is a composite of death, disabling stroke, and life-threatening bleed.

[e] The tertiary net clinical outcome is a composite of death, stroke, systemic embolic event, and life-threatening bleed.

than patients allocated to edoxaban, 30 mg. These higher bleeding rates with edoxaban, 60 mg, in older patients were not offset by reduced rates of ischemic stroke.

Standard-dose direct oral anticoagulants (DOACs) may introduce excessive bleeding risk in patients 80 years and older without a benefit in efficacy.[25,26] ENVISAGE-TAVI AF (Edoxaban vs Standard of Care and Their Effects on Clinical Outcomes in Patients Having Undergone Transcatheter Aortic Valve Implantation–Atrial Fibrillation) was a randomized clinical trial comparing the HDER (edoxaban, 60/30 mg daily as in ENGAGE AF-TIMI 48) vs vitamin K antagonists (VKAs) in patients with AF and aortic stenosis after transcatheter aortic valve replacement (TAVR).[22] Of the 1426 participants, most were octogenarians or older (mean age, 82.1 years, similar to our current analysis); 54% did not meet criteria for dose reduction and thus received 60 mg, whereas 46% were dose-reduced to 30 mg. HDER was noninferior to VKAs for the composite of all-cause death, myocardial infarction, ischemic stroke or SEE, valve thrombosis, or major bleeding. However, patients randomized to HDER had a 40% higher risk of major bleeding compared with VKAs, attributable to a more than doubling in the risk of major gastrointestinal bleeding.

Although reasons for increased bleeding with HDER in the ENVISAGE-TAVI trial remain to be fully understood, it is notable that most patients enrolled were older adults with no dose-reduction criteria, and up to 60% of patients received concomitant antiplatelet drugs during the trial. Thus, we believe that 60 mg of edoxaban, the approved dose for patients without any of the 3 aforementioned dose-reduction criteria, may have been excessive in this older adult high-risk population undergoing TAVR. Furthermore, studies have shown that patients with aortic stenosis have an intrinsic higher bleeding risk because of acquired von Willebrand disease[27] and a higher incidence of gastrointestinal angiodysplasia (Heyde syndrome).[28] Notably, in the ENVISAGE-TAVI AF trial, edoxaban, 30 mg, significantly decreased all-cause mortality by 36% vs VKAs in patients with dose-reduction criteria. In patients without dose-reduction criteria, mortality was numerically, but not significantly, 20% higher with edoxaban, 60 mg, vs VKAs.

The use of lower than recommended doses of DOACs is common,[8-10] with rates of 11% to 23% in global registries.[29,30] Underdosing is more frequent in patients who are older and have more comorbidities.[29,30] Notably, inappropriate use of lower doses of DOACs is associated with higher rates of ischemic events and all-cause mortality.[8,31,32]

Our analyses show that patients 80 years and older without dose-reduction criteria treated with edoxaban, 30 mg, instead of 60 mg experienced approximately 9 fewer major gastrointestinal bleeding events for each additional ischemic stroke. Furthermore, preventing bleeding may have long-term implications for efficacy: in the ENGAGE AF-TIMI 48 trial, patients who interrupted oral anticoagulation after a bleeding event were at a markedly higher risk of ischemic events and death.[33,34] In the context of prior studies, these results suggest that edoxaban, 30 mg, once daily may represent a reasonable approach in patients 80 years and older with AF at increased risk of bleeding, regardless of the presence or absence of currently labeled dose-reduction criteria.[13,14,22,26]

The future of precision medicine in anticoagulation involves selecting the right drug and dose for each patient.[35] In the case of older patients, this is particularly challenging because of the independent association of older age with events that may be prevented by, caused by anticoagulation, or occur despite anticoagulation.[15] Furthermore, patients may have different levels of drug exposure because of differences in age, kidney or liver function, drug-drug interactions, and body weight. Finally, patients (and clinicians) may weigh the consequences of ischemic and bleeding events differently. The present analyses provide data that are a step in the direction of precision dosing of anticoagulants in older patients.

Limitations

This study has some limitations. This was a post hoc analysis with no adjustment for multiple comparisons, which inflates the risk

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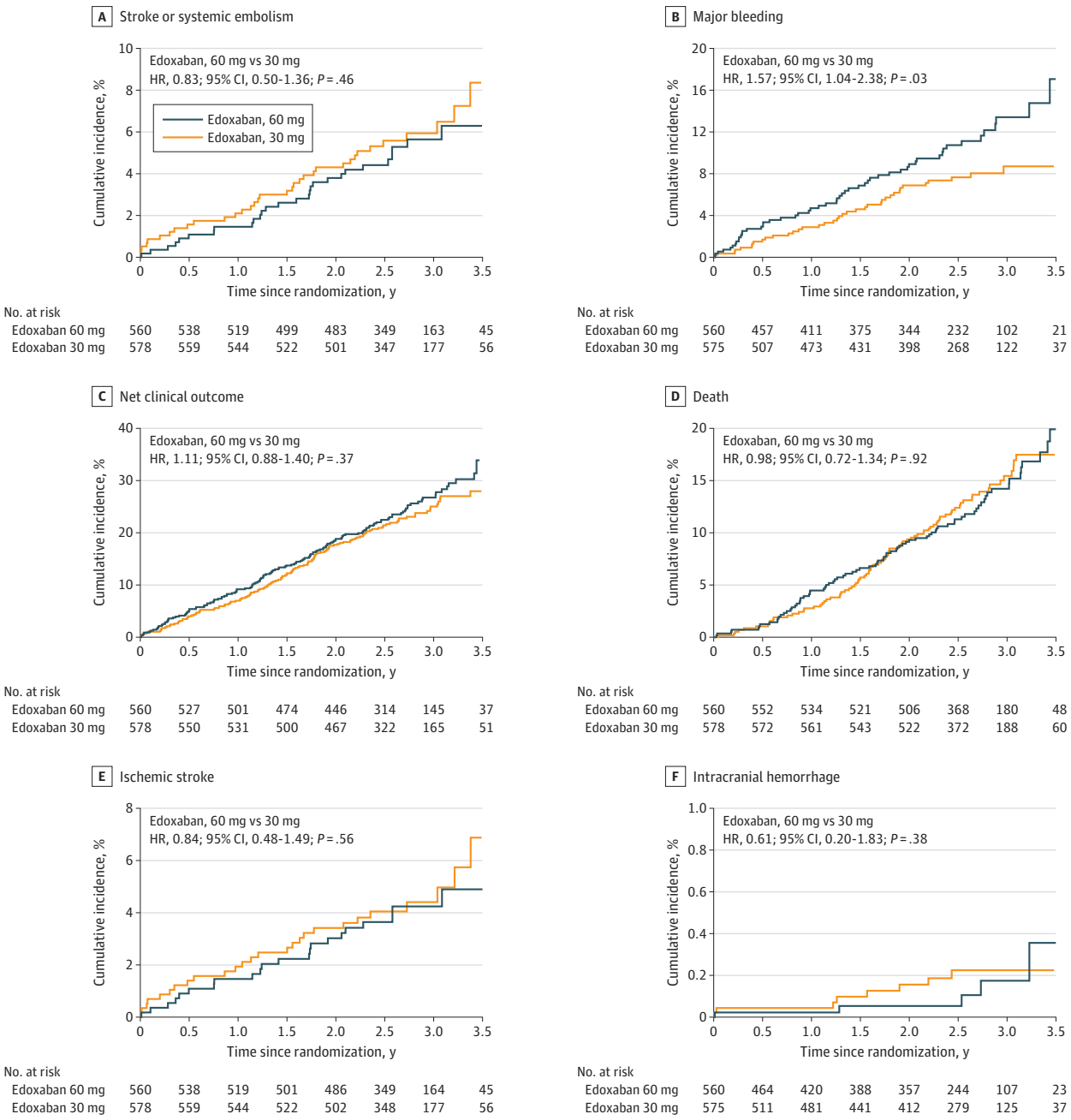
Figure 2. Efficacy and Safety Outcomes of Edoxaban, 60 mg vs 30 mg, in Patients 80 Years and Older With No Dose-Reduction Criteria



Cumulative event rates are shown for stroke or systemic embolism (A), major bleeding (B), the primary net clinical outcome of stroke, systemic embolic event, major bleeding, or death from any cause (C), death from any cause (D), ischemic stroke (E), and intracranial hemorrhage (F). HR indicates hazard ratio.

of type I and type II errors. Therefore, although the main analysis herein describes a comparison of patients enrolled in a randomized clinical trial, results should be considered exploratory. Moreover, clinical trial participants usually represent a more compliant subset of the target population. Patients 80 years and older from the ENGAGE AF-TIMI 48 trial who were treated with warfarin had a median time in therapeutic range of 69.5%, higher than that reported in prior similar trials and most observational studies. It is uncertain how well our findings may be generalized, although it is reasonable to infer that, because of treatment interactions and the need for active monitoring, management of VKAs would be more challenging than with edoxaban in clinical practice.[36,37] Additionally, sharp dichotomies rarely exist in biology, and the 80-year cutoff used in this analysis should be interpreted in the context of patient characteristics and individual decision-making. Further, the ENGAGE AF-TIMI 48 trial had strict entry criteria, and results should not be extrapolated to patients who were ineligible for the trial. Ran-

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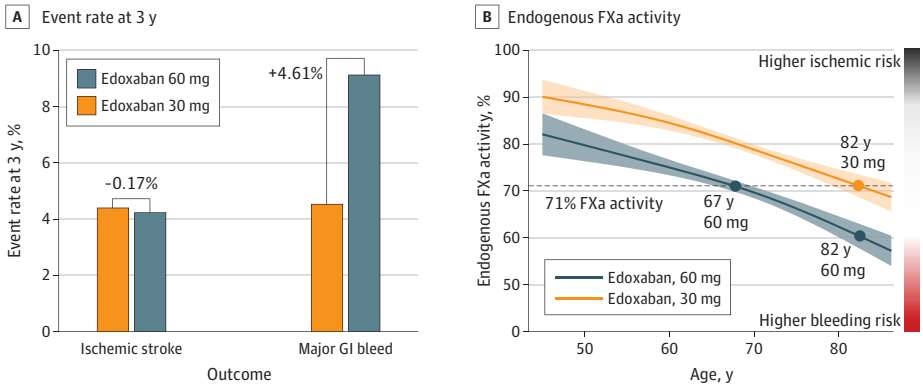
Figure 3. Pharmacodynamic and Clinical Outcomes in Patients with No Dose-Reduction Criteria



A, Absolute difference in ischemic stroke and major gastrointestinal bleeding at 3 years for patients 80 years and older without dose-reduction criteria randomized to edoxaban, 60 mg (n = 560) vs 30 mg (n = 578). Event rates were calculated using Kaplan-Meier estimates. Patients 80 years and older randomized to edoxaban, 60 mg, had higher rates of major gastrointestinal bleeding (hazard ratio [HR], 2.24; 95% CI, 1.29-3.90; *P* = .004) with no significant differences in ischemic stroke (HR, 0.84; 95% CI, 0.48-1.49; *P* = .56) compared with edoxaban, 30 mg. B, Endogenous factor Xa (FXa) activity at trough by age. Lower values indicate greater anticoagulant effect. Line graph indicates the predicted endogenous FXa activity at trough by age in patients without dose-reduction criteria randomized to edoxaban, 60 mg (n = 5251) vs 30 mg (n = 5249). The predicted FXa activity at trough declined with age and was 8.0% to 11.4% lower for edoxaban, 60 mg (vs edoxaban, 30 mg) across the age range. In patients without dose-reduction criteria, the predicted FXa activity of 71% at trough in a 67-year-old patient taking edoxaban, 60 mg, was similar to that of an 82-year-old patient taking 30 mg. GI indicates gastrointestinal.

domized clinical trials evaluating lower doses of anticoagulants in older patients are needed.[1]

Conclusions

In a secondary analysis of the ENGAGE AF-TIMI 48 trial including patients 80 years and older without dose-reduction criteria, rates of major bleeding events, in particular gastrointestinal hemorrhage, were lower with edoxaban, 30 mg, compared with edoxaban, 60 mg, without an increase in the rate of ischemic events. Additionally, among patients 80 years and older with or without dose-reduction criteria, net clinical outcomes, major bleeding, intracranial hemorrhage, and death were lower with edoxaban, 30 mg, compared with warfarin, with similar rates of stroke or SEE, ischemic stroke, and major gastrointestinal bleeding. These data suggest that lower-dose anticoagulants, such as edoxaban, 30 mg once daily, may be considered in all patients 80 years and older with AF irrespective of dose-reduction criteria.

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Concept and design: Zimerman, Braunwald, Steffel, Chen, Antman, Giugliano.
Acquisition, analysis, or interpretation of data: Zimerman, Steffel, Van Mieghem, Palazzolo, Murphy, Chen, Unverdorben, Ruff, Giugliano.
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