

Randomized, Double-Blind Comparison of Half-Dose Versus Full-Dose Edoxaban in 14,014 Patients With Atrial Fibrillation



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ABSTRACT

BACKGROUND In the ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48) trial, the lower dose edoxaban regimen (LDER) and the higher dose edoxaban regimen (HDER) were noninferior to well-managed warfarin for stroke prevention in atrial fibrillation.

OBJECTIVES The objective of the present analysis of the ENGAGE AF-TIMI-48 trial was to comprehensively compare the net clinical outcome (NCO) of LDER (30 mg once daily, dose reduced to 15 mg in selective patients) versus HDER (60 mg once daily, dose reduced to 30 mg in selective patients).

METHODS This study performed a pre-specified analysis of the ENGAGE AF-TIMI 48 trial, comparing patients on LDER versus HDER.

RESULTS The pre-defined primary NCO (stroke/systemic embolism [SEE], major bleeding, death) was less frequent with LDER (7.26% vs. 8.01%; hazard ratio: 0.90; 95% confidence interval: 0.84 to 0.98; $p = 0.014$). The secondary (disabling stroke, life-threatening bleeding, or all-cause mortality) and tertiary pre-defined NCOs (stroke, SEE, life-threatening bleeding, or all-cause mortality) were similar between the 2 dosing regimens. Patients randomized to LDER versus HDER had a significantly higher risk of stroke/SEE (2.04% vs. 1.56%; hazard ratio: 1.31; 95% confidence interval: 1.12 to 1.52; $p < 0.001$). Conversely, major bleeding, intracranial hemorrhage, major gastrointestinal bleeding, and life-threatening bleeding occurred significantly less frequently with LDER compared with those of HDER. These findings were supported by multiple pharmacokinetic findings.

CONCLUSIONS In the ENGAGE AF-TIMI 48 trial, the primary NCO was reduced with LDER versus HDER, whereas the secondary and tertiary NCOs were similar between the 2 dosing regimens. These results may aid physicians in evidence-based individualization of edoxaban dosing. However, the approved HDER remains the standard therapy among the available edoxaban dosing regimens for stroke prevention in atrial fibrillation. (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48 [ENGAGE AF-TIMI 48]; [NCT00781391](https://doi.org/10.1016/j.jacc.2020.12.053)) (J Am Coll Cardiol 2021;77:1197-207) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).



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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AUC_{0–24,ss} = area under the concentration-time curve from time zero to 24 h at steady state

CI = confidence interval

C_{min} = trough levels

C_{max} = peak levels

DOAC = direct oral anticoagulants

HDER = higher dose edoxaban regimen

HR = hazard ratio

LDER = lower dose edoxaban regimen

NCO = net clinical outcome

SEE = systemic embolic event

Direct oral anticoagulants (DOACs) have become the preferred therapy for stroke prevention in atrial fibrillation (AF), based on the outcomes of 4 pivotal phase III randomized clinical trials (1–8). Although they demonstrated at least similar (if not better) efficacy regarding stroke prevention, the risk of severe (including intracranial and fatal) bleeding was reduced compared with warfarin (2). As such, current guidelines recommend DOACs over vitamin K antagonists for stroke prevention in most patients with AF (7,8). However, the inherent risk of severe bleeding, although less frequent with DOAC therapy than vitamin K antagonists, may affect the morbidity and mortality of patients (9,10).

The fear of bleeding has resulted in a substantial overuse of unstudied “off label” reduced doses of all DOACs (11–14). However,

there are no randomized clinical trial data to allow for any assessment of efficacy or safety of reduced doses of apixaban or rivaroxaban in patients who do not fulfill the respective pre-defined dose-reduction criteria (4,5). In contrast, in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial, warfarin was compared with 2 doses of dabigatran (150 mg twice daily and 110 mg twice daily) corresponding to a 27% decrease in dose with the lower dose of dabigatran versus higher dose of dabigatran (3). Although the 150 mg twice daily dose of dabigatran provided superior efficacy over warfarin in reducing stroke and systemic embolic events (SEE) at a similar rate of major bleeding, the 110 mg twice daily dose was similarly effective as warfarin at a lower rate of major bleeding.

In the double-blind, 3-arm randomized ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48) trial, both the higher dose (HDER) and lower dose edoxaban regimens (LDER), which represent a 50% reduction in dose, were non-inferior to well-managed warfarin for the prevention of stroke/SEE in patients with AF (6). Although both regimens significantly reduced the risk of major bleeding and cardiovascular death, LDER increased the incidence of ischemic stroke by 41% compared with warfarin. Efficacy was preserved in patients who had their dose reduced per protocol compared with similar patients in the warfarin arm, whereas dose reduction provided an even greater relative reduction in major bleeding (15). These data led to the approval of HDER (but not LDER) for stroke prevention in patients with AF worldwide.

Importantly, a statistically significant reduction in all-cause mortality was observed with LDER compared with warfarin, raising the possibility that this dosing regimen might be beneficial for certain patient profiles. The present analysis of ENGAGE AF-TIMI-48 was performed to compare the on-treatment outcomes of patients on LDER versus HDER. In ENGAGE AF-TIMI 48, 3 measures for the net clinical outcome (NCO) were pre-defined, combining the most relevant efficacy and safety endpoints. The NCOs could represent a better metric of the value of a novel treatment strategy because it takes a more integrative, comprehensive approach towards overall patient outcome rather than separately focusing on single events (e.g., ischemic stroke or major bleeding) (16). In the present analysis, we therefore comprehensively compared the effects of LDER and HDER on the primary, secondary and tertiary NCOs.

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METHODS

STUDY POPULATION AND ENDPOINTS. The design and main results of the phase III, double-blind, double-dummy ENGAGE AF-TIMI 48 trial have been reported previously (6,17). In brief, 21,105 patients with AF at moderate to high risk of stroke (CHADS₂ score ≥ 2) were randomized to receive HDER (60 mg once daily), LDER (30 mg once daily), or warfarin. In patients with moderate renal insufficiency (creatinine clearance 30 to 50 ml/min as estimated by the Cockcroft-Gault equation), body weight ≤60 kg, or in those who required concomitant use of the strong P-glycoprotein inhibitors quinidine, verapamil, or dronedarone, the edoxaban dose was reduced by 50% (HDER: 60 to 30 mg; LDER: 30 mg to 15 mg) (17). The primary efficacy endpoint of the trial was stroke/SEE; other efficacy endpoints included ischemic stroke, hemorrhagic stroke, and all-cause and cardiovascular mortality (6). The principal safety endpoint was major bleeding as defined by the International Society on Thrombosis and Hemostasis (18); other safety outcomes included clinically relevant nonmajor bleeding and intracranial hemorrhage (17). The protocol and amendments were approved by the ethics committee at each participating center. All patients provided written informed consent.

The 3 pre-defined composite NCOs of the trial were: 1) stroke, SEE, major bleeding, or all-cause mortality; 2) disabling stroke, life-threatening bleeding, or all-cause mortality; and 3) stroke, SEE, life-threatening bleeding, or all-cause mortality (6).

Disabling ischemic strokes were those graded by the investigators as Rankin scale 3 to 5 (19), whereas a

score of 6 denoted a fatal stroke. Life-threatening bleeding was defined as an intracranial hemorrhage (including hemorrhagic stroke and subdural or epidural hemorrhages) or a bleeding event that resulted in hemodynamic compromise that required intervention. Fatal bleeding events were those in which bleeding directly resulted in death (17). All bleeding events (including their location and severity), strokes, cardiovascular events (including stroke, SEE, and myocardial infarction), and deaths were adjudicated by a central clinical endpoint committee that was unaware of treatment assignment.

STATISTICAL ANALYSIS. The statistical analyses presented in the present report were conducted in the modified intention-to-treat population restricted to the LDER and HDER arms. Patients randomized to warfarin and 45 patients randomized to edoxaban who did not receive any edoxaban after randomization were excluded. Analysis of bleeding endpoints for safety analyses were performed while on-treatment (between the first dose and +3 days after the last dose or final visit, whichever occurred first). Analysis of efficacy and NCO endpoints (including bleeding components of NCOs) were assessed during the overall study follow-up from the first dose through the last visit.

Pharmacokinetic exposure measures in individual patients, including the steady-state trough (C_{\min}), average (C_{avg}), and peak (C_{\max}) edoxaban concentrations, as well as the area under the concentration-time curve from time zero to 24 h at steady state ($\text{AUC}_{0-24,ss}$), were derived by a population pharmacokinetic modeling. The median and 5th to 95th percentile values are summarized for each dose group.

Baseline characteristics are presented as median (interquartile range) for continuous variables and frequencies for categorical variables. Event rates are expressed per 100 patient-years. Hazard ratios (HRs) with 95% confidence intervals (CIs) comparing LDER versus HDER were calculated using a Cox proportional hazards model. The Cox proportional hazards assumption was tested and verified using Schoenfeld residuals. All tests were 2-sided with a p value <0.05 considered to be significant without adjustment for multiple comparisons. Because the trial was not powered for subgroup analyses, the results herein are considered exploratory. The Thrombolysis In Myocardial Infarction Study Group has an independent copy of the trial database and conducted all analyses. Analyses were performed with SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina).

RESULTS

BASELINE CHARACTERISTICS. There were no significant differences in the baseline characteristics of patients randomized to LDER ($n = 7,002$) versus HDER ($n = 7,012$), except for a slightly lower prevalence of chronic heart failure in patients randomized to LDER (56.6% vs. 58.3%; $p = 0.043$) and valvular heart disease in patients randomized to HDER (20.2% vs. 21.7%; $p = 0.032$) (Table 1).

EDOXABAN PLASMA LEVELS IN PATIENTS RECEIVING LDER AND HDER. C_{\min} , C_{avg} , and C_{\max} edoxaban levels, as well as the $\text{AUC}_{0-24,ss}$, are shown for patients on standard dose HDER (60 mg) and LDER (30 mg), as well as dose-reduced HDER (30 mg) and LDER (15 mg) (Figure 1, Supplemental Table 1). An approximate 3-fold difference in edoxaban plasma levels was observed across a 4-fold difference in edoxaban dose exposure. These findings were in line with the previously observed pharmacodynamic effects in patients who received LDER and HDER, which resulted in corresponding increases in anti F-Xa activity (15,20).

OUTCOMES OF LDER VERSUS HDER. The risk of reaching a primary NCO event (stroke or SEE, major bleeding, or death) over a median follow-up of 2.8 years was significantly reduced with LDER compared with HDER (7.26% vs. 8.01%; HR: 0.90; 95% CI: 0.84 to 0.98; $p = 0.014$) (Central Illustration, Figure 2). No difference between the 2 treatment groups was observed in the incidence of the secondary (composite of disabling stroke, life-threatening bleeding, or all-cause mortality) or tertiary NCOs (composite of stroke, SEE, life-threatening bleeding, or all-cause mortality).

In line with the main outcome comparing edoxaban with warfarin in the ENGAGE AF-TIMI 48 trial (6), patients randomized to LDER versus HDER had a significantly higher risk of reaching the primary study endpoint of stroke or SEE (2.04% vs. 1.56%; HR: 1.31; 95% CI: 1.12 to 1.52; $p < 0.001$) (Central Illustration, Figure 2). This difference was driven primarily by a 43% increase in ischemic strokes (1.77% vs. 1.24%; HR: 1.43; 95% CI: 1.21 to 1.69; $p < 0.001$) with LDER. In the same way, all strokes (1.92% vs. 1.48%; HR: 1.3; 95% CI: 1.11 to 1.52; $p = 0.001$) as well as systemic embolic events (0.15% vs. 0.08%; HR: 1.92; 95% CI: 1.03 to 3.59; $p = 0.040$), were significantly higher with LDER versus HDER.

In contrast, disabling and fatal strokes were similar between the 2 treatment groups (0.81% vs. 0.69%; HR: 1.18; 95% CI: 0.94 to 1.49; $p = 0.16$). Major bleeding

TABLE 1 Baseline Characteristics of Patients Treated With LDER Versus HDER

	Overall	LDER (n = 7,002)	HDER (n = 7,012)	p Value
Age, yrs	72 (64-78)	72 (64-78)	72 (64-78)	0.90
Age ≥75 yrs	5,627 (40.2)	2,789 (39.8)	2,838 (40.5)	0.44
Female	5,377 (38.4)	2,718 (38.8)	2,659 (37.9)	0.28
Race: Asian	1,931 (13.8)	975 (13.9)	956 (13.6)	0.62
Weight, kg	82 (70-95)	81.6 (70-95)	82 (70-95)	0.59
Weight <55 kg	637 (4.5)	326 (4.7)	311 (4.4)	0.53
Current smoker	1,011 (7.2)	514 (7.3)	497 (7.1)	0.56
Stroke/TIA	3,967 (28.3)	1,999 (28.5)	1,968 (28.1)	0.53
Diabetes	5,083 (36.3)	2,533 (36.2)	2,550 (36.4)	0.81
Congestive heart failure	8,048 (57.4)	3,962 (56.6)	4,086 (58.3)	0.043
Hypertension	13,113 (93.6)	6,545 (93.5)	6,568 (93.7)	0.64
Coronary artery disease	4,685 (33.4)	2,358 (33.7)	2,327 (33.2)	0.54
Permanent AF	7,213 (51.5)	3,593 (51.3)	3,620 (51.6)	0.72
Paroxysmal AF	3,574 (25.5)	1,827 (26.1)	1,747 (24.9)	0.11
Valvular heart disease	2,931 (20.9)	1,516 (21.7)	1,415 (20.2)	0.032
Carotid disease	863 (6.2)	440 (6.3)	423 (6.0)	0.54
Hepatic disease	581 (4.1)	292 (4.2)	289 (4.1)	0.89
History of Malignancy	914 (6.5)	456 (6.5)	458 (6.5)	0.96
Peptic ulcer disease	876 (6.3)	459 (6.6)	417 (5.9)	0.14
Vascular disease	5,248 (37.4)	2,638 (37.7)	2,610 (37.2)	0.58
Increased risk of falling	592 (4.2)	283 (4.0)	309 (4.4)	0.28
VKA-naïve	5,736 (40.9)	2,857 (40.8)	2,879 (41.1)	0.76
CHA ₂ DS ₂ -VASc score	4 (3.0-5.0)	4 (3.0-5.0)	4 (3.0-5.0)	0.94
Score >3	9,976 (71.2)	4,987 (71.2)	4,989 (71.1)	0.92
CrCl, mL/min	70.3 (53.8-92.2)	70.3 (53.8-92.2)	70.4 (53.8-92.4)	0.94
CrCl ≤50 mL/min	2,697 (19.2)	1,325 (18.9)	1,372 (19.6)	0.33
Any antiplatelet	4,403 (31.4)	2,168 (31.0)	2,235 (31.9)	0.25
Aspirin	4,069 (29.0)	2,009 (28.7)	2,060 (29.4)	0.37
SBP >150 mm Hg	1,073 (7.7)	565 (8.1)	508 (7.3)	0.067
LVEF <30%	495 (4.8)	243 (4.7)	252 (4.9)	0.65

Values are median (interquartile range) or n (%).

AF = atrial fibrillation; CrCl = creatine clearance; HDER = higher-dose edoxaban regimen; LDER = lower-dose edoxaban regimen; LVEF = left ventricular ejection fraction; SBP = systolic blood pressure; TIA = transient ischemic attack; VKA = vitamin K antagonist.

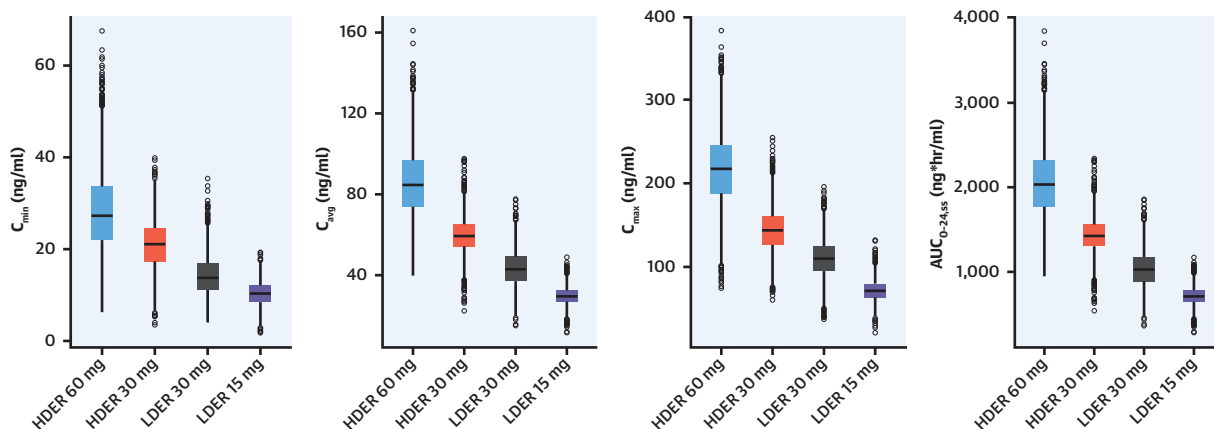
(1.82% vs. 2.87%; HR: 0.64; 95% CI: 0.55 to 0.74; $p < 0.001$), as well as intracranial hemorrhage (0.25% vs. 0.38%; HR: 0.65; 95% CI: 0.44 to 0.97; $p = 0.035$), major gastrointestinal bleeding (0.87% vs. 1.53%; HR: 0.57; 95% CI: 0.46 to 0.70; $p < 0.0001$), and fatal and/or life-threatening bleeding (0.38% vs. 0.62%; HR: 0.61; 95% CI: 0.44 to 0.84; $p = 0.002$) all occurred less frequently with LDER versus HDER (Figure 2).

SUBGROUP ANALYSIS OF PATIENT OUTCOMES WITH LDER VERSUS HDER. No significant interactions were observed for the primary NCO across 16 pre-specified subgroups (Supplemental Figure 1A). In patients with a history of malignancy ($n = 914$; 6.5%), the occurrence of a secondary (Supplemental Figure 1B) or a tertiary NCO (Supplemental Figure 1C) was significantly lower for LDER versus HDER, whereas there was no difference between the 2 dosing regimens in patients without a history of

malignancy. The reduction in stroke and SEE with HDER versus LDER was consistent across all subgroups investigated (Supplemental Figure 2). Conversely, no relevant interactions were observed for any subgroup of patients regarding the significant reduction in major bleeding with LDER versus HDER (Supplemental Figure 3).

EFFECT OF DOSE REDUCTION ON PATIENT OUTCOME. Twenty-five percent of patients qualified for dose reduction at randomization as specified in the protocol. Patients who received the reduced doses of LDER (i.e., 15 mg) versus HDER (i.e., 30 mg) had even lower risks for hemorrhagic stroke and for intracranial hemorrhage compared with the risk reductions observed in patients who did not have dose reduction (i.e., edoxaban 30 mg vs. 60 mg) (Figure 3). There were no significant interactions by dose reduction status for the remainder of the endpoints

FIGURE 1 Edoxaban Exposure Measures in Patients Who Received LDER and HDER



Trough (C_{\min}), average (C_{avg}), and peak (C_{\max}) edoxaban concentrations, as well as the area under the concentration-time curve from time zero to 24 h at steady state ($AUC_{0-24,ss}$), are shown for patients on standard dose higher-dose edoxaban regimen (HDER) (60 mg), dose-reduced HDER (30 mg), standard dose lower-dose edoxaban regimen (LDER) (30 mg) and dose-reduced LDER (15 mg). Boxes show the median and interquartile range of data. Whiskers represent the extent of data within 1.5 times the interquartile range. Points represent data outside the whiskers.

(Figure 2), including strokes, other bleeding events, and the NCOs.

DISCUSSION

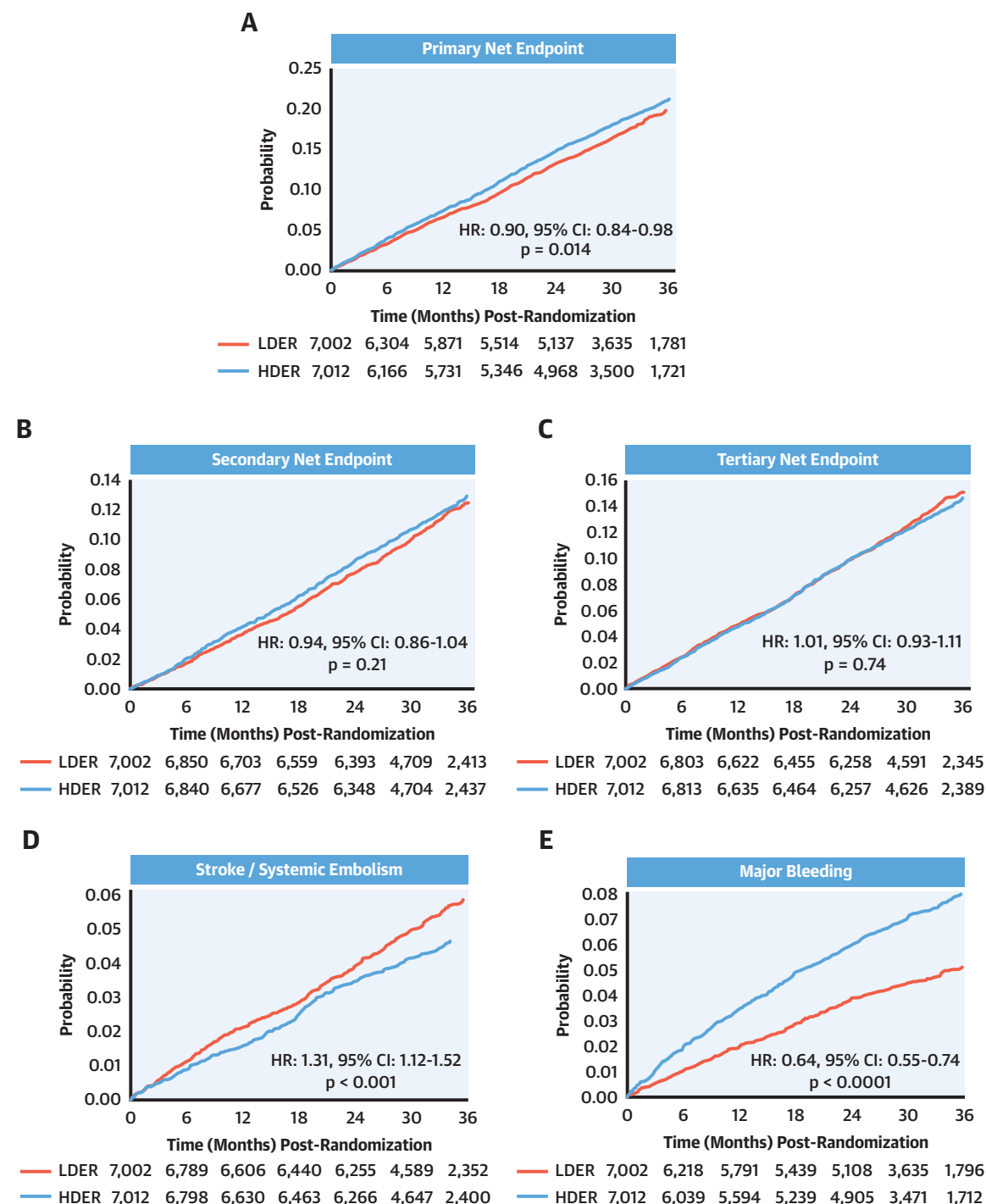
In the present analysis, we comprehensively compared patients randomly assigned to LDER or HDER in the ENGAGE AF-TIMI 48 trial. In the on-treatment population the occurrence of a primary NCO event was significantly less likely with LDER versus HDER, whereas the secondary and tertiary predefined NCOs were similar in both groups (Supplemental Figure 4). Therefore, from a NCO perspective, both dosing regimens represented reasonable anticoagulant choices. Ischemic events (including the primary efficacy endpoint of stroke/SEE) occurred significantly more often with LDER versus HDER, which was counterbalanced by significantly fewer major bleedings (including fatal or life-threatening, as well as major gastrointestinal bleedings) with LDER.

Our data are in line with the results from the ELDERCARE-AF (Edoxaban low-dose for elder care AF patients) trial, which compared the use of 15 mg edoxaban once daily versus placebo in Japanese octogenarians deemed ineligible for oral anticoagulation (21). In these patients, edoxaban 15 mg reduced the risk of stroke by an absolute 4.4%/year (2.3%/year vs. 6.7%/year, HR: 0.34; 95% CI: 0.19 to 0.61; $p < 0.001$) at the cost of a nonsignificant absolute increase of 1.5%/year in major bleeding

(3.3%/year vs. 1.8%/year; HR: 1.87; 95% CI: 0.90 to 3.89; $p = 0.09$). It remains to be determined how these results in patients considered inappropriate for standard dose anticoagulant translate into non-Japanese populations and other clinical situations. Nevertheless, these results are of great value because they represent the only large placebo-controlled randomized clinical trial data in this difficult-to-treat patient population, thereby indicating that a low dose of edoxaban does exhibit relevant, potent anticoagulant effects and does confer a degree of protection from stroke in AF.

A superior benefit of a lower (vs. higher) dose of a DOAC is consistent with outcomes from other patient populations (e.g., after acute coronary syndromes). In the ATLAS-ACS (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome - Thrombolysis In Myocardial Infarction) 2 trial, ultra-low-dose rivaroxaban (2.5 mg twice daily), but not low-dose rivaroxaban (5 mg twice daily), resulted in a reduction in all-cause mortality when added to antiplatelet therapy in patients after an acute coronary syndrome without AF (22). Similarly, patients with chronic coronary or peripheral vascular disease included in the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial derived a significant net clinical benefit from ultra-low-dose rivaroxaban (2.5 mg twice daily) plus aspirin, but not low-dose rivaroxaban (5 mg twice daily), compared with aspirin monotherapy (23,24).

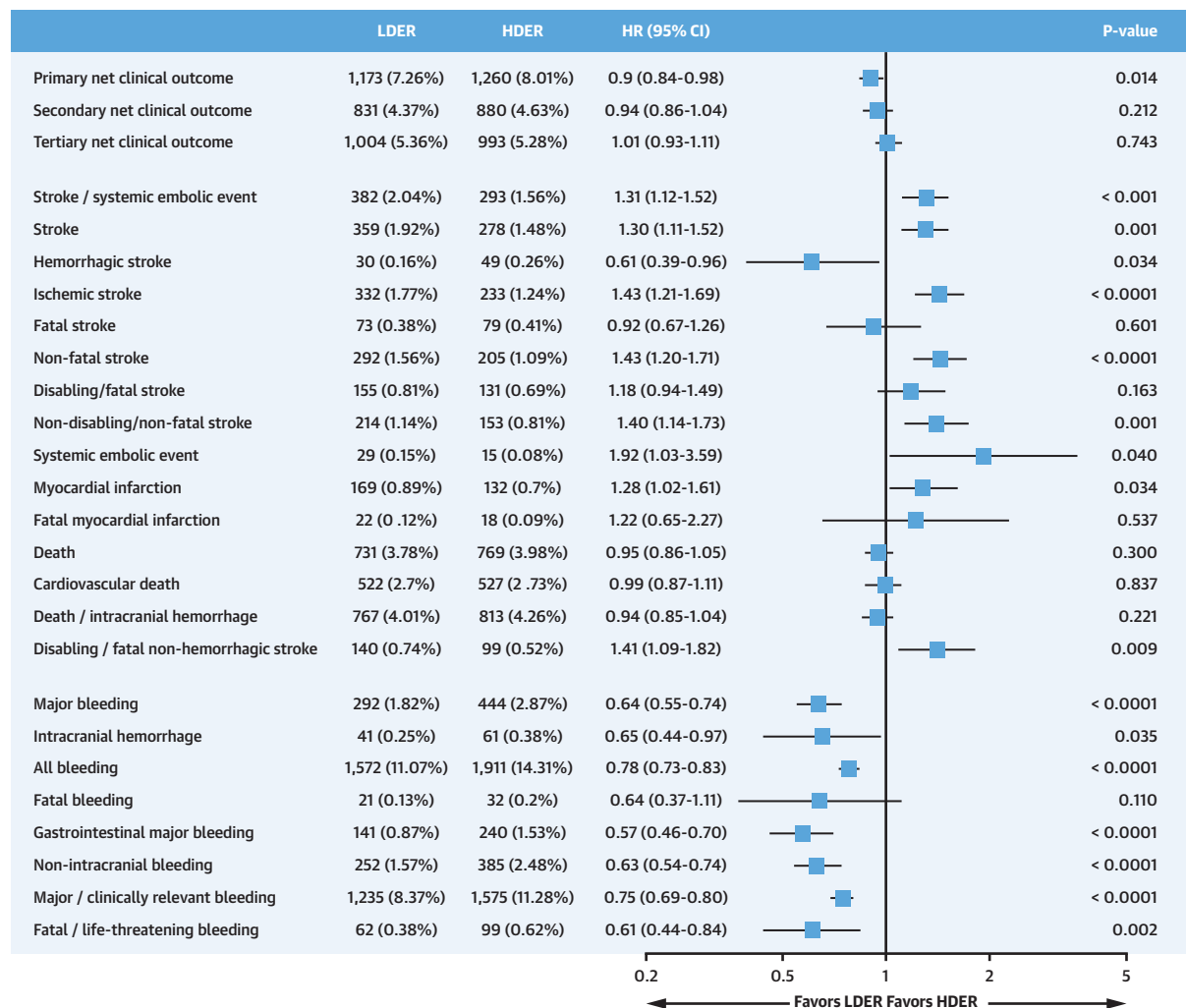
CENTRAL ILLUSTRATION Outcomes on Lower-Dose Edoxaban Regimen (LDER; Red) Versus Higher-Dose Edoxaban Regimen (HDER; Blue) in the ENGAGE AF-TIMI 48 Trial



Steffel, J. et al. J Am Coll Cardiol. 2021;77(9):1197-207.

Event rates are shown for the (A) primary (stroke, stroke/systemic embolism [SEE], major bleeding, or all-cause mortality), (B) secondary (disabling stroke, life-threatening bleeding, or all-cause mortality), and (C) tertiary net clinical outcomes (stroke, SEE, life-threatening bleeding, or all-cause mortality), as well as for (D) stroke and systemic embolism and (E) major bleeding. CI = confidence interval; HDER = higher-dose edoxaban regimen; HR = hazard ratio; LDER = lower-dose edoxaban regimen.

FIGURE 2 Outcomes With LDER Versus HDER

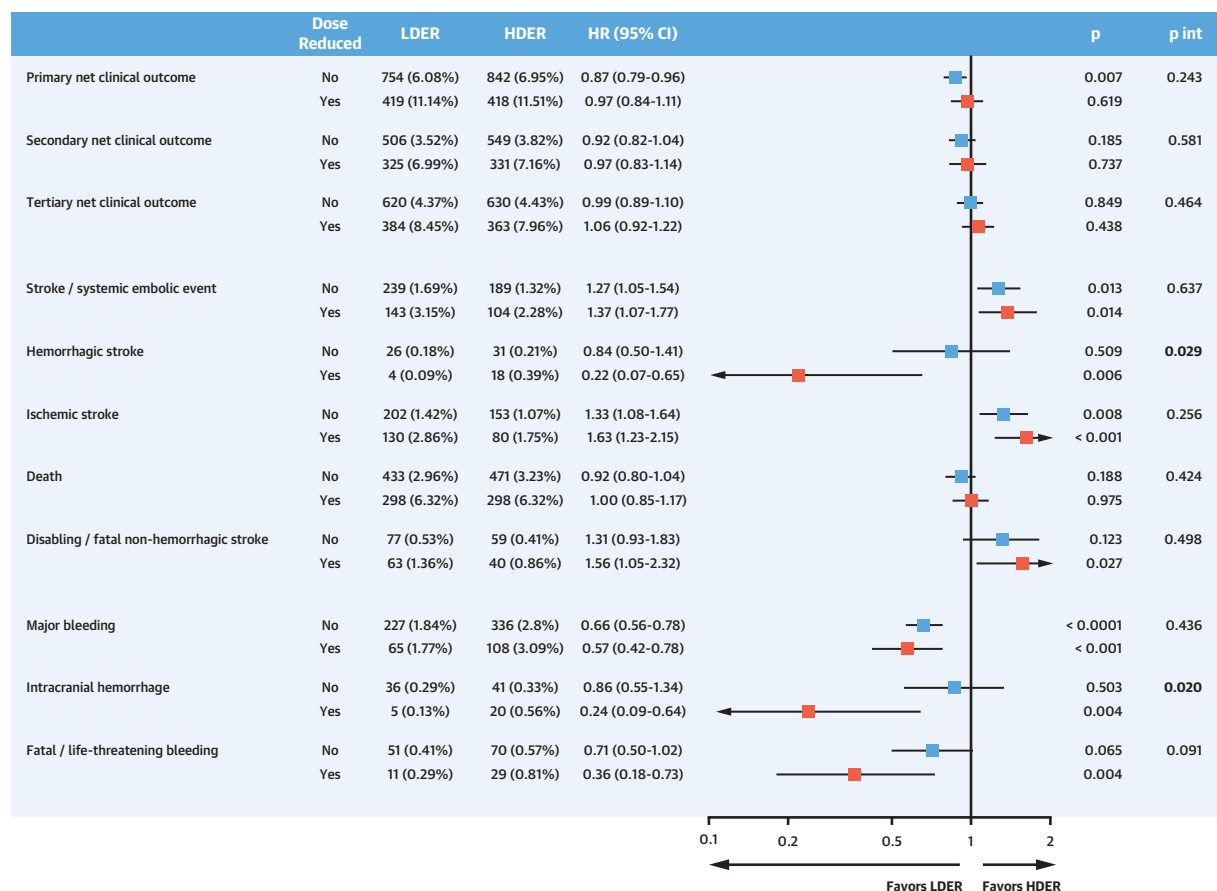


Analysis of net clinical outcome and efficacy endpoints on overall study follow-up in a modified intention-to-treat (mITT) population that excluded subjects who never took any study drug. Analysis of safety endpoints in the on-treatment period in the mITT population that excluded subjects who never took any study drug. CI = confidence interval; HR = hazard ratios; other abbreviations as in Figure 1.

Evaluation of net outcomes have been proposed to address the overall benefit of DOACs to allow for a more integrative assessment of risk benefit rather than separately focusing on single events such as ischemic stroke or major bleeding (16). Patients with AF on anticoagulation are frequently at risk of both severe ischemic and bleeding events, both of which need to be considered to evaluate the value of any anticoagulant therapy. One criticism of previous NCOs has been the difference in clinical severity and degree of comorbidity that may exist between the individual components (25). Thus, for the present analysis, 3 net outcomes were pre-defined, with the

secondary and tertiary net outcomes combining the most severe ischemic and bleeding events that could occur in patients with AF on oral anticoagulation. The integration of these most serious disease- and anti-coagulation therapy-related outcomes acknowledged the fact that not every ischemic stroke leads to the same clinical consequence; conversely, the range of major bleeding complications is even wider, and clinical consequences vary substantially. Therefore, our present analysis might more adequately reflect the value of edoxaban regimens compared with the top-line weighting of the reduction in primary efficacy versus an increase in principal safety endpoints,

FIGURE 3 Net Clinical Outcome, Efficacy, and Safety Events by Dose-Reduction Status LDER Versus HDER



Red squares = dose reduced; blue squares = not dose reduced. Abbreviations as in Figures 1 and 2.

which has many important shortcomings related largely to the mismatch in the clinical significance of such events.

This might also be important from a patient perspective because observational and survey data indicated that patients demonstrated a strong aversion to severe strokes; this may differ from the perspective of physicians (26,27). In our analysis, disabling and fatal strokes (i.e., the most severe consequences of AF) were similar between both dosing regimens, which indicated that from a patient perspective, both dosing regimens could represent a valid treatment option. In contrast, fatal or life-threatening bleedings (i.e., the most severe complications of anticoagulation therapy) were fewer with LDER compared with that of HDER.

The differences in edoxaban dosing regimens, which represented a 4-fold difference in total daily dose, translated into a 2- to 3-fold difference in

achieved drug concentrations (15). Levels achieved in patients who had dose reductions were consistently lower than those in patients who did not have dose reduction, despite the presence of at least 1 dose reduction criterion that previously demonstrated an increase in edoxaban levels. Dose reduction by 50% in patients with moderate renal impairment was performed to avoid excessive exposure to edoxaban (which is 50% renally cleared) compared with patients without renal impairment. Because patients with renal impairment are at increased risk for bleeding for a number of reasons (e.g., greater burden of comorbidities, increased vascular fragility, platelet dysfunction), the intention was not to exactly match exposure between both patient populations but aimed to ensure levels that on average were modestly lower to avoid excess exposure in these vulnerable patients. This included trough edoxaban plasma levels (C_{min}), which were shown to best correlate with

bleeding events (28). These findings might at least partly explain the even greater reduction in hemorrhagic stroke and intracranial hemorrhage observed in patients who received dose-reduced LDER versus HDER compared with those who received standard dose LDER versus HDER. In the present work, we demonstrated that the described pharmacokinetics extended to the modeled area under the curve for drug exposure, which correlated best with the efficacy of edoxaban (20).

Patients with AF and malignancy are being increasingly anticoagulated with DOACs, primarily due to the positive signals from dedicated studies that have indicated better outcomes with DOACs over low-molecular weight heparin in this population for the treatment and prevention of venous thromboembolism (29–31). In exploratory subgroup analyses, patients with a history of malignancy had a lower likelihood of reaching a secondary or tertiary NCO on LDER versus that of HDER. Although active malignancy was an exclusion criterion for patients included in the ENGAGE AF-TIMI 48 trial, 914 (6.5%) patients had a remote history of malignancy. These patients had significantly higher rates of major bleeding, whereas strokes or systemic embolic events were similar compared with patients without a previous malignancy. A similar pattern was observed in patients with a history of malignancy included in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial (32). In this patient population, the risk of bleeding could represent a particularly pronounced driver of the more favorable result with LDER regarding the primary NCO. It is conceivable that in addition to the tumor itself, various co-existing conditions associated with an increased risk of bleeding contribute to this, including a higher incidence of frailty and/or increased risk of falling (6.7% vs. 4.2%) (Table 1) (33), a lower hematocrit and/or platelet count (34), and more frequent use of medications that interact with DOACs or pre-dispose to bleeding (35–37). However, in view of the post hoc nature of this particular analysis and the low number of events, these findings need to be interpreted with great caution and should be viewed as hypothesis-generating.

Our findings have important practical implications, especially in the light of current clinical practice of DOAC prescription patterns, which show a substantial overuse of lower doses not according to the label and not prospectively tested in randomized trials (11,12,14). A recent analysis from the GARFIELD (Global Anticoagulant Registry in the FIELD) registry, which included 10,426 DOAC-treated patients, revealed

underdosing in 23.2%, which was associated with an increase incidence of cardiovascular mortality (13). A U.S. national registry of patients with AF demonstrated that of patients who received a reduced dose DOAC, 57% of the time dosing was not in accordance with the U.S. Food and Drug Administration label (38). Similar high rates of off-label use of low-dose DOACs were reported in a systematic review of 75 observational studies from across the globe and were associated with an increased risk of mortality (39). Reasons for off-label use are manifold but almost invariably relate to a higher weighting of the inherent risk of bleeding (frequently perceived as an iatrogenic event) over the risk of ischemic stroke (40,41). However, there are no randomized clinical trial data to allow for any assessment of efficacy or safety of the reduced dose of apixaban, dabigatran (75 mg twice daily), or rivaroxaban in patients who do not fulfill the respective pre-defined dose reduction criteria. Observational data indicated an up to 4.8-fold higher incidence in ischemic events with no benefit in terms of bleeding for patients who received off-label, dose-reduced DOACs (12,38,42). Residual confounding was likely in these analyses and the limited availability of only nonrandomized data makes adequate patient informed consent and shared decision-making challenging when proposing a lower dose DOAC.

In contrast, although not approved, LDER was studied in >7,000 patients with AF as part of the randomized, double-blind, ENGAGE AF-TIMI 48 trial. Therefore, use of LDER might allow for evidence-based shared decision-making between health care providers and patients based on randomized clinical trial data. In conjunction with the results of the ELDERCARE-AF trial (21), use of LDER might represent a reasonable approach for stroke prevention in AF in the presence of legitimate concerns about an increased risk of bleeding.

STUDY LIMITATIONS. The primary pre-specified analysis of the double-blind randomized ENGAGE AF-TIMI 48 trial included comparisons of each regimen of edoxaban to warfarin. Thus, the present analysis should be interpreted as hypothesis-generating. These data were derived from patients enrolled in a clinical trial with strict entry criteria, and our results might not apply to all patients encountered in clinical practice. We did not adjust for multiple comparisons and acknowledge that the trial was not powered for subgroup analyses. Nonetheless, our results were derived from 14,014 patients randomized to 1 of 2 different edoxaban regimens. The findings were consistent with other (pre-defined) subanalyses from the ENGAGE AF-TIMI 48 trial, as well as other DOAC trials, which lend further validity

to our findings. Use of lower-dose edoxaban (i.e., 30 mg once daily in patients without a dose reduction and 15 mg once daily in patients with at least 1 dose reduction criterion) is not approved for use in patients with AF. Thus, patients and payers need to be informed before treatment initiation, including the anticipated effects based on the results of the ENGAGE AF-TIMI 48 trial.

CONCLUSIONS

In ENGAGE AF-TIMI 48, patients randomized to LDER had a lower risk of reaching the primary NCO compared with those on HDER, whereas the secondary and tertiary NCOs occurred to a similar degree in both arms. Together with the directionally similar results from the ELDERCARE-AF trial, these results could aid physicians in evidence-based individualization of edoxaban dosing. Similar studies with other DOACs would be welcome, particularly in light of the frequent off-label use of untested and unapproved low-dose DOACs in clinical practice. However, the approved DOAC dosing regimens remain the standard of care for stroke prevention in AF.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: Approved dosing regimens for target-specific DOACs have become a standard of care for stroke prevention in patients with AF, yet underdosing is common in clinical practice. In a randomized trial, the lower-dose edoxaban regimen was associated with a higher risk of stroke or systemic embolism than the higher-dose edoxaban regimen but showed lower rates of bleeding and the composite endpoint of major bleeding, stroke and systemic embolism, and mortality.

TRANSLATIONAL OUTLOOK: Additional randomized trials are needed to determine whether these findings extend to other DOACs and to help guide individualization of DOAC dosing.

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APPENDIX For supplemental figures and table, please see the online version of this paper.