

Edoxaban Versus Warfarin in Latin American Patients With Atrial Fibrillation

The ENGAGE AF-TIMI 48 Trial

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ABSTRACT

BACKGROUND There is limited information about the use of antithrombotic therapies and outcomes of Latin American (LatAm) subjects with atrial fibrillation. The global ENGAGE AF-TIMI 48 (Effective Anticoagulation With Factor Xa Next Generation Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48) trial compared the efficacy and safety of edoxaban versus warfarin over a median follow-up of 2.8 years.

OBJECTIVES The authors aimed to compare adjusted outcomes in Latin America versus outside Latin America and to compare outcomes stratified by anticoagulant treatment and region.

METHODS The authors analyzed clinical characteristics and outcomes, adjusted for baseline characteristics, the Human Development Index, and randomized treatment of 2,661 LatAm versus 18,444 non-Latin American subjects (nLAS).

RESULTS When compared with nLAS, LatAm subjects had a similar overall risk for stroke. After multivariate adjustment, the risks of stroke/systemic embolism (hazard ratio [HR]: 1.19; 95% confidence interval [CI]: 0.96 to 1.47; $p = 0.11$) and major bleeding (HR: 1.10; 95% CI: 0.89 to 1.36; $p = 0.39$) were similar in LatAm and nLAS. LatAm subjects were at higher adjusted risk of death (HR: 1.48; 95% CI: 1.30 to 1.69; $p < 0.001$) and intracranial hemorrhage (ICH) (HR: 1.55; 95% CI: 1.00 to 2.41; $p = 0.049$). In both regions, when compared with warfarin, edoxaban reduced stroke/systemic embolism (HR: 0.64 and 0.91 in LatAm and nLAS, respectively), major bleeding (HR: 0.71 and 0.82), and cardiovascular death (HR: 0.78 and 0.88), without evidence of regional heterogeneity ($p_{\text{int}} = 0.41, 0.50, \text{ and } 0.70$, respectively). There was a greater reduction in hemorrhagic stroke with edoxaban in LatAm (HR: 0.16) than in nLAS (HR: 0.64; $p_{\text{int}} = 0.037$).

CONCLUSIONS After multivariable adjustment, LatAm subjects with atrial fibrillation had higher rates of intracranial hemorrhage and death than nLAS. Outcomes with higher-dose edoxaban versus warfarin were at least as favorable in LatAm subjects as in nLAS, with an even greater reduction in hemorrhagic stroke seen in LatAm. (J Am Coll Cardiol 2018;72:1466-75) © 2018 Published by Elsevier on behalf of the American College of Cardiology Foundation.



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The prevalence of atrial fibrillation (AF) increases with aging and is associated with a higher risk of ischemic stroke, heart failure, and all-cause mortality (1–3). The international ENGAGE AF-TIMI 48 (Effective Anticoagulation With Factor Xa Next Generation Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48) trial evaluated, in a double-blind fashion, 2 different dose regimens of edoxaban, an oral anti-factor Xa inhibitor, compared with warfarin in 21,105 subjects with AF who were at moderate to high risk of stroke. Both edoxaban dose regimens were noninferior to warfarin in stroke prevention and significantly reduced rates of major and intracranial bleeding and cardiovascular (CV) death (4).

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Data regarding baseline characteristics and outcomes of Latin American (LatAm) subjects with AF are limited. There is considerable variability in the available data from LatAm, depending on the design of global registries and numbers of centers and countries involved (5–7). Although the rate of prescription of vitamin K antagonists (VKAs) in LatAm is similar to that reported in North American and European surveys, there is scarce information about the efficacy and safety of antithrombotic therapies in this population (8).

In this paper, we analyzed baseline characteristics and outcomes with edoxaban versus warfarin in subjects with AF enrolled in the ENGAGE AF-TIMI 48 trial in LatAm compared with non-Latin American subjects (nLAS).

METHODS

STUDY DESIGN. The design of ENGAGE AF-TIMI 48 has been described (9). This international trial randomized subjects with documented AF in a double-blind manner to 3 treatment arms: higher-dose edoxaban (HDE) (60 mg daily), lower-dose edoxaban (LDE) (30 mg daily), and warfarin with dose adjustment to achieve an international normalized ratio (INR) 2.0 to 3.0. The doses of edoxaban were reduced by 50% in both edoxaban treatment arms in cases with a creatinine clearance ≤ 50 ml/min, low body weight (≤ 60 kg), or concomitant drug therapy with a strong

P-glycoprotein inhibitor. Median follow-up was 2.8 years (8). For this analysis, we focused on HDE because this is the regimen approved for use.

SUBJECTS ENROLLED. Eligible subjects were age 21 years or older with a documented episode of AF within the prior 12 months and a CHADS₂ score ≥ 2 , who required permanent oral anticoagulation. Exclusion criteria included a history of AF secondary to a reversible disorder, creatinine clearance below 30 ml/min at the end of screening, moderate to severe mitral stenosis, previous implantation of mechanical valves, need for dual antiplatelet therapy, high risk of bleeding, coronary revascularization, or stroke within the previous 30 days.

OUTCOMES. The primary efficacy outcome was the time to first stroke (ischemic or hemorrhagic) or systemic embolic event (SEE). The secondary efficacy outcome was the composite of stroke, SEE, or death from CV causes (including bleeding). Major adverse cardiovascular events (MACE) were stroke, SEE, myocardial infarction (MI), or death from any cause. Additional efficacy endpoints were death from any cause, MI, and the individual elements described in the previous text.

The principal safety outcome was major bleeding as defined by the International Society of Thrombosis and Haemostasis. Key secondary safety outcomes included fatal, life-threatening, intracranial, and clinically relevant nonmajor bleeding. The primary net clinical outcome was a composite of stroke, SEE, and major bleeding.

Differences in baseline characteristics and outcomes between regions (LatAm vs. nLAS) were compared first in the whole population (collapsing across all 3 randomized treatment groups). This was followed by comparisons of outcomes by region within the warfarin arm only. Finally, outcomes were compared by randomized treatment (edoxaban vs. warfarin), stratified by region.

Adjudication of all events was performed by an independent clinical endpoint committee that was unaware of study drug assignment. The relevant ethics committee at each center reviewed and

ABBREVIATIONS AND ACRONYMS

AF	= atrial fibrillation
HDE	= higher-dose edoxaban
ICH	= intracranial hemorrhage
INR	= International Normalized Ratio
LatAm	= Latin American
LDE	= lower-dose edoxaban
nLAS	= non-Latin American subjects
SEE	= systemic embolism
TTR	= time in therapeutic range
VKA	= vitamin K antagonists

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TABLE 1 Baseline Characteristics of Latin American and Non-Latin American Subjects		
	Non-Latin America (n = 18,444)	Latin America (n = 2,661)
Age, yrs	70.5 ± 9.4	71.4 ± 9.7
≥75 yrs	7,308 (39.6)	1,166 (43.8)
Male	11,485 (62.3)	1,580 (59.4)
Body weight, kg	84.8 ± 20.5	77.3 ± 16.6
≤60 kg	1,721 (9.3)	382 (14.4)
Creatinine clearance, ml/min	77.1 ± 31.6	70.7 ± 28.3
≤50 ml/min	3,351 (18.2)	622 (23.4)
Pattern of atrial fibrillation		
Permanent	9,151 (49.6)	1,714 (64.4)
Persistent	4,315 (23.4)	553 (20.8)
Paroxysmal	4,972 (27.0)	394 (14.8)
Comorbidities		
Congestive heart failure	10,438 (56.6)	1,686 (63.4)
Left ventricular ejection fraction, <40%*	1,939/14,156 (13.7)	364/1,408 (25.9)
Hypertension	17,221 (93.4)	2,533 (95.2)
Systolic blood pressure, mm Hg	130.2 ± 15.1	129.4 ± 16.5
Diastolic blood pressure, mm Hg	77.7 ± 9.9	78.2 ± 10.3
Diabetes mellitus	6,866 (37.2)	758 (28.5)
Previous stroke/transient ischemic attack	5,179 (28.1)	794 (29.8)
Prior MI	2,262 (12.3)	171 (6.4)
Prior PAD	779 (4.2)	62 (2.3)
Prior MI or PAD	2,840 (15.4)	223 (8.4)
CHADS ₂ score	2.8 ± 1.0	2.9 ± 1.0
CHADS ₂ /DS ₂ -VASC score	4.3 ± 1.4	4.2 ± 1.4
Charlson Comorbidity Index	2.8 ± 1.1	2.7 ± 1.0
Socioeconomic indexes		
Human Development Index in 2010	0.83‡ ± 0.09	0.76† ± 0.05
Gross National Index in 2010, \$	26,934 ± 14,640	12,170 ± 2,806
Medications		
Dose reduction at randomization	4,572 (24.8)	784 (29.5)
Previous use of vitamin K antagonists ≥60 days	11,165 (60.5)	1,276 (48.0)
Medications at baseline		
Beta-blocker	12,391 (67.2)	1,593 (59.9)
Renin, angiotensin, or aldosterone inhibitor	11,971 (64.9)	1,935 (72.7)
Calcium-channel blockers	6,089 (33.0)	490 (18.4)
Lipid lowering	9,328 (50.6)	754 (28.3)
Diuretic agents	10,999 (59.6)	1,657 (62.3)
Digitalis	5,350 (29.0)	977 (36.7)
Amiodarone	1,972 (10.7)	520 (19.5)

Values are mean ± SD or n (%). p < 0.001 for each comparison, except for male sex (p = 0.004), systolic blood pressure (p = 0.003), diastolic blood pressure (p = 0.020), previous stroke/transient ischemic attack (p = 0.060), and diuretic agents (p = 0.009). *Comparison of left ventricular ejection fraction does not include 1,253 Latin American and 4,288 non-Latin American subjects for whom data on left ventricular function were not available. †Similar to the Human Development Indices of Uruguay, Libya, and Panama in 2010 or 53rd highest among 169 countries. ‡Similar to the Human Development Indices of the Czech Republic and Slovenia in 2010 or 29th highest among 169 countries.

CHADS₂ = congestive heart failure, hypertension, age ≥75 years (2 points), diabetes mellitus, prior stroke or transient ischemic attack; CHA₂DS₂-VASC = congestive heart failure; hypertension; age ≥75 years (2 points); diabetes mellitus; prior stroke, transient ischemic attack, or thromboembolism (2 points); vascular disease; age 65-74 years; sex category (female); MI = myocardial infarction; PAD = peripheral artery disease.

in LatAm versus nLAS with a chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. Event rates were expressed per 100 patient-years. Mortality was reported using a Kaplan-Meier curve stratified by treatment arm and region. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated with Cox proportional hazards models.

Because subjects were enrolled from different parts of the world, the patterns of comorbidities, sociocultural levels, incomes, and access to health care facilities might differ. Therefore, all proportional hazards analyses comparing LatAm subjects to nLAS were adjusted for age; sex; body mass index; history of hypertension, dyslipidemia, diabetes, stroke or transient ischemic attack (TIA), congestive heart failure (CHF), coronary artery disease (CAD), hepatic disease, and bleeding (excluding intracranial hemorrhage); smoking status; increased risk of falling; risk of neuropsychiatric disease; race; creatinine; pattern of atrial fibrillation; alcohol intake; medication predisposing to bleeding; as well as the randomized treatment and the Human Development Index (HDI). The HDI was created to emphasize that people and their capabilities should be the ultimate criteria for assessing the development of a country, not economic gross national index alone (10). In 2010, the HDI was available for 169 countries, which were grouped in quartiles as very high (HDI >0.788), high (0.677 to 0.784), medium (0.488 to 0.669), or low (0.300 to 0.470). Proportional hazards derived from Cox models comparing edoxaban and warfarin treatment were adjusted for the 2 randomization stratification factors as described in the ENGAGE AF-TIMI 48 protocol—need for dose reduction, and CHADS₂ score at randomization. The proportional hazards assumption was confirmed with Schoenfeld residuals and by plotting the log negative-log of the survival function by log of time.

Analyses for efficacy events were calculated using the intention-to-treat principle, which included data from subjects who underwent randomization, and included all events whether occurring on or off study drug during the treatment period. Analyses for bleeding events were performed during the on-treatment period, defined as the time between the first study drug dose and either the end of the planned treatment period or 3 days after the last dose of study drug if it was discontinued early, with interval censoring of events during study drug interruptions that lasted >3 days. Analyses were done using SAS version 9.4 (SAS Institute, Cary, North Carolina). This trial is registered with ClinicalTrials.gov (NCT00781391).

approved the protocol and amendments, and all patients provided written informed consent.

STATISTICAL ANALYSIS. Baseline characteristics and concomitant medications at randomization were summarized as counts and percentages or means with SDs. These were compared between subjects enrolled

TABLE 2 Outcomes in Latin American Versus Non-Latin American Subjects (Pooled Treatment Arms)

	Overall Events (n = 21,105)		LatAm Events (n = 2,661)		nLAS Events (n = 18,444)		Unadjusted Model		Adjusted Model*	
	n	%/yr	n	%/yr	n	%/yr	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
Efficacy endpoints										
Stroke or systemic embolic event	1,016	1.80	135	2.08	881	1.77	1.17 (0.98-1.40)	0.090	1.19 (0.96-1.47)	0.11
Stroke	958	1.70	124	1.91	834	1.67	1.13 (0.94-1.37)	0.19	1.16 (0.93-1.44)	0.20
Hemorrhagic	169	0.30	23	0.35	146	0.29	1.20 (0.77-1.87)	0.41	1.49 (0.90-2.48)	0.12
Ischemic	804	1.42	102	1.56	702	1.40	1.11 (0.90-1.37)	0.32	1.09 (0.85-1.40)	0.48
Systemic embolic event	67	0.12	14	0.21	53	0.10	2.02 (1.13-3.63)	0.018	2.06 (1.01-4.19)	0.047
Myocardial infarction	443	0.78	38	0.58	405	0.81	0.72 (0.51-1.00)	0.051	0.90 (0.59-1.37)	0.62
Cardiovascular hospitalization	5,621	11.45	583	9.87	5,038	11.67	0.84 (0.77-0.91)	<0.001	0.95 (0.86-1.06)	0.37
Death	2,349	4.05	437	6.56	1,912	3.72	1.81 (1.63-2.01)	<0.001	1.48 (1.30-1.69)	<0.001
Cardiovascular death	1,668	2.87	312	4.68	1,356	2.64	1.81 (1.60-2.04)	<0.001	1.43 (1.22-1.67)	<0.001
Noncardiovascular death	681	1.17	125	1.88	556	1.08	1.82 (1.50-2.22)	<0.001	1.76 (1.37-2.26)	<0.001
Cardiovascular death, stroke, systemic embolic event	2,355	4.17	387	5.94	1,968	3.94	1.52 (1.37-1.70)	<.0001	1.33 (1.16-1.52)	<0.001
Major adverse cardiac event†	2,666	4.76	414	6.40	2,252	4.55	1.42 (1.28-1.58)	<0.001	1.28 (1.12-1.46)	<0.001
Safety endpoints										
Major bleeding	1,196	2.59	146	2.67	1,050	2.58	1.01 (0.85-1.20)	0.91	1.10 (0.89-1.36)	0.39
Life-threatening or fatal bleeding	335	0.71	53	0.96	282	0.68	1.38 (1.03-1.86)	0.030	1.36 (0.93-1.97)	0.11
Intracranial hemorrhage	234	0.50	38	0.69	196	0.47	1.43 (1.01-2.02)	0.044	1.55 (1.00-2.41)	0.049
Gastrointestinal bleeding	551	1.18	73	1.32	478	1.16	1.11 (0.86-1.41)	0.43	1.14 (0.82-1.56)	0.44
Major or CRNM bleeding	4,450	10.63	513	10.26	3,937	10.68	0.94 (0.85-1.03)	0.17	1.22 (1.09-1.37)	<0.001
Any bleeding	5,478	13.66	638	13.22	4,840	13.72	0.94 (0.87-1.02)	0.14	1.26 (1.14-1.40)	<0.001
Net clinical outcomes‡										
Primary	4,033	7.38	593	9.32	3,440	7.13	1.31 (1.20-1.43)	<0.001	1.27 (1.14-1.41)	<0.001
Secondary	2,708	4.75	480	7.31	2,228	4.42	1.69 (1.53-1.86)	<0.001	1.45 (1.28-1.64)	<0.001
Tertiary	3,132	5.56	518	7.98	2,614	5.25	1.54 (1.40-1.69)	<0.001	1.38 (1.23-1.56)	<0.001

Efficacy endpoints and net clinical outcomes were calculated using intention-to-treat for the overall population. Safety events are calculated in the on-treatment population (see text for details). The safety cohort consisted of 21,026 patients, 2,651 from Latin America (LatAm) and 18,375 from non-Latin America (nLAS). *Adjusted for age, sex, body mass index, history of hypertension, history of dyslipidemia, history of diabetes, smoking, increased risk of falling, risk of neuropsychiatric disease, race, creatinine, history of stroke or transient ischemic attack, history of congestive heart failure, pattern of atrial fibrillation, history of coronary artery disease, history of hepatic disease, history of bleeding (excluding intracranial hemorrhage), alcohol intake, medication predisposing to bleeding, 2010 Human Development Index, and randomized treatment. †Major adverse cardiovascular event, including myocardial infarction, stroke, systemic embolic event, and death due to cardiovascular causes (including bleeding). ‡The primary net clinical outcome was a composite of stroke, systemic embolic event, major bleeding, or death from any cause. The secondary net clinical outcome was a composite of disabling stroke, life-threatening bleeding, or death from any cause. The tertiary net clinical outcome was an exploratory composite of stroke, systemic embolic event, life-threatening bleeding, or death from any cause.

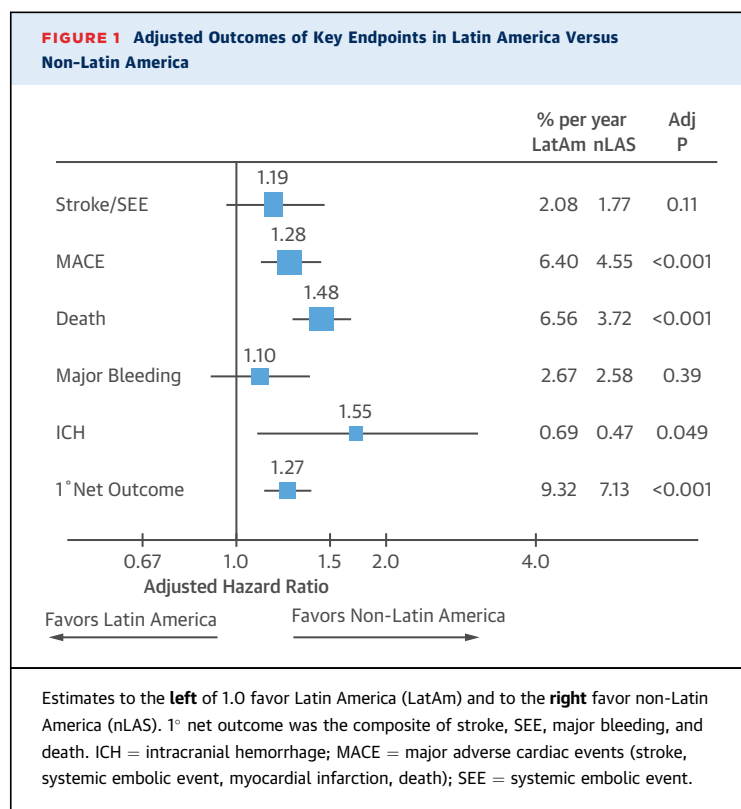
CI = confidence interval; CRNM = clinically relevant nonmajor.

RESULTS

PATIENT CHARACTERISTICS. The ENGAGE AF-TIMI 48 trial recruited 21,105 subjects worldwide, including 2,661 subjects from 7 LatAm countries: Argentina (n = 1,060), Brazil (n = 707), Chile (n = 254), Colombia (n = 141), Guatemala (n = 136), Mexico (n = 190), and Peru (n = 173). Baseline characteristics of LatAm subjects compared with nLAS are shown in [Table 1](#). LatAm subjects had higher proportions of permanent AF, elderly subjects, higher proportions of pre-existing hypertension, CHF, left ventricular ejection fraction <40%, and lower mean creatinine clearance and body weight ([Table 1](#)). On the other hand, LatAm subjects had a lower incidence of prior MI, diabetes and peripheral artery disease (PAD). Both the mean CHA₂DS₂-VASc score and Charlson Comorbidity Index were slightly (0.1 points), yet significantly, lower in LatAm subjects ([Table 1](#)). Meanwhile, the mean HDI

and Gross National Index in LatAm were 8% and 55% lower, respectively, compared with the other countries combined. LatAm subjects were less likely to have received VKAs prior to randomization and to be treated at baseline with beta-blockers, statin, and calcium-channel blockers, but were more frequently treated with amiodarone, digitalis, diuretic agents, and renin-angiotensin-aldosterone inhibitors (p < 0.01 for each).

STUDY DRUG MANAGEMENT. A total of 10 LatAm subjects (0.4%) and 69 nLAS (0.4%) never took study drug and thus were not included in the safety population. The study drug was interrupted for >3 days less frequently in LatAm subjects than nLAS (47.9% vs. 52.2%; p < 0.001) during the median 2.8 years of follow-up. The median time in therapeutic range (TTR) in patients randomized to warfarin was significantly lower in LatAm subjects (66% vs. 69%; p < 0.001).



OUTCOMES IN THE TOTAL POPULATION. The primary efficacy endpoint of stroke/SEE occurred in 135 of 2,661 patients enrolled in LatAm compared with 881 of 18,444 nLAS (2.08%/year vs. 1.77%/year in LatAm vs. nLAS, respectively; adjusted HR: 1.19; 95% CI: 0.96 to 1.47; $p = 0.11$) (Table 2, Figure 1). There were no regional differences in the adjusted risk of all stroke or stroke subtypes, myocardial infarction, or hospitalization for CV causes (Table 2).

The adjusted risk of major bleeding was also similar in LatAm versus nLAS (2.67%/year vs. 2.58%/year; adjusted HR: 1.10; 95% CI: 0.89 to 1.36; $p = 0.39$) (Table 2, Figure 1). However, the adjusted risks of intracranial hemorrhage (ICH) (adjusted HR: 1.55; 95% CI: 1.00 to 2.41; $p = 0.049$), major or clinically relevant nonmajor bleeding (adjusted HR: 1.22; 95% CI: 1.09 to 1.37; $p < 0.001$), and all bleeding (adjusted HR: 1.26; 95% CI: 1.14 to 1.40; $p < 0.001$) were significantly increased in LatAm.

All-cause mortality was significantly higher in LatAm (6.56%/year vs. 3.72%/year; adjusted HR: 1.48; 95% CI: 1.30 to 1.69; $p < 0.001$), with an excess risk in both deaths due to CV (4.68%/year vs. 2.64%/year; adjusted HR: 1.43; 95% CI: 1.22 to 1.67) and non-CV causes (1.88%/year vs. 1.08%/year; adjusted HR: 1.76; 95% CI: 1.37 to 2.26); $p < 0.001$ for each (Table 2,

Figure 1). A similar pattern was observed for major adverse CV events and the 3 net clinical outcomes that combined death, CV events, and bleeding.

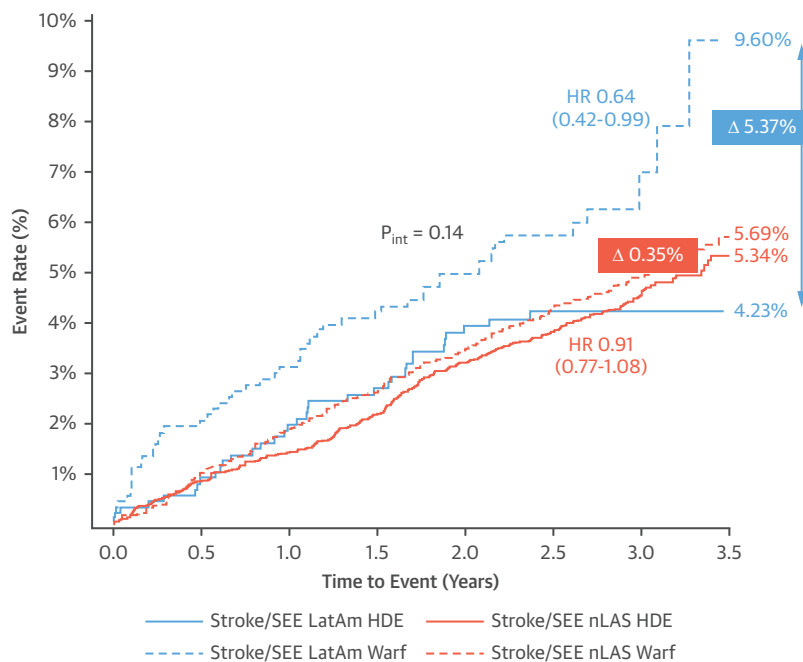
There was variation in event rates between the countries in LatAm, but, because of the small sample size in several countries, it is not possible to determine whether these were play of chance or not. When analyzing causes of CV deaths, we found that sudden cardiac death (adjusted HR: 1.48; 95% CI: 1.18 to 1.86) and death due to heart failure or shock (adjusted HR: 2.20; 95% CI: 1.64 to 2.95) were significantly more frequent in LatAm subjects (each $p \leq 0.001$). Among non-CV deaths, fatal infections/sepsis were significantly more common (adjusted HR: 3.09; 95% CI: 2.13 to 4.48; $p < 0.001$) in LatAm subjects. There were no other significant differences among other causes of CV and non-CV deaths between regions.

There was evidence for a significant interaction between the use of baseline lipid therapy and CV mortality between the regions. Among patients treated with lipid-lowering drugs, the CV mortality was similar in LatAm versus nLAS (adjusted HR: 1.14; 95% CI: 0.88 to 1.48), whereas among patients who were not on lipid-lowering therapy at baseline, CV mortality was significantly higher in LatAm subjects (adjusted HR: 1.56; 95% CI: 1.30 to 1.86; $p_{\text{int}} = 0.033$). No other significant interactions between regions or other therapies, including the prior use of VKAs or baseline use of beta-blockers, calcium-channel blockers, digitalis, or amiodarone, were present for the endpoint of CV death ($p_{\text{int}} > 0.10$ for each).

EFFICACY AND SAFETY OUTCOMES IN 7,036 SUBJECTS RANDOMIZED TO WARFARIN. In the warfarin arm, the rates of stroke/SEE were 2.50%/year in the 888 LatAm subjects versus 1.71%/year in the 6,148 nLAS (adjusted HR: 1.45; 95% CI: 1.01 to 2.09; $p = 0.042$), while all-cause mortality rates were 7.34%/year versus 3.97%/year (adjusted HR: 1.49; 95% CI: 1.19 to 1.85; $p < 0.001$) (Online Table 1). In the warfarin arm, there was no difference in major bleeding (adjusted HR: 1.15; 95% CI: 0.84 to 1.58; $p = 0.38$) by region, although LatAm subjects did have higher adjusted risks of ICH (adjusted HR: 2.07; 95% CI: 1.18 to 3.65; $p = 0.011$) and life-threatening or fatal bleed (adjusted HR: 1.83; 95% CI: 1.13 to 2.96; $p = 0.014$) (Online Table 1).

EFFICACY AND SAFETY IN 14,071 SUBJECTS RANDOMIZED TO HDE VERSUS WARFARIN BY REGION. The annualized rates of stroke/SEE in the 1,774 LatAm subjects and in the 12,297 nLAS were both lower with HDE compared with warfarin (LatAm: HDE 1.61% vs. warfarin 2.50%; HR: 0.64; 95% CI: 0.42

FIGURE 2 Kaplan-Meier Curve for Stroke/SEE Stratified By Region and Treatment



Subjects randomized in Latin America are shown in **orange** and non-Latin American subjects in **blue**. The **solid line** indicates subjects randomized to higher-dose edoxaban, and the **dashed line** warfarin. HDE = higher-dose edoxaban; HR = hazard ratio; Warf = warfarin; other abbreviations as in [Figure 1](#).

to 0.99; nLAS: HDE 1.56% vs. warfarin 1.71%; HR: 0.91; 95% CI: 0.77 to 1.08) with no statistical evidence of heterogeneity by region ($p_{\text{int}} = 0.14$) ([Table 3](#), [Online Table 2](#), [Central Illustration](#)). There was a larger absolute reduction in the Kaplan-Meier rate of stroke/SEE at 3.5 years with HDE compared to warfarin in LatAm subjects (5.37%) than in nLAS (0.35%) ([Figure 2](#)). Annualized rates for LatAm of all-cause mortality were 7.34% versus 6.47% for nLAS, HR: 0.88 (95% CI: 0.70 to 1.10, $p_{\text{int}} = 0.27$). HDE significantly reduced hemorrhagic stroke compared with warfarin in both regions, but there was evidence of significant effect modification by region ($p_{\text{int}} = 0.037$), with a greater benefit observed in LatAm subjects (HR: 0.16; 95% CI: 0.05 to 0.55) compared with nLAS (HR: 0.64; 95% CI: 0.44 to 0.92). In both regions, HDE tended to reduce the rates of MACE and CV mortality compared with warfarin ([Table 3](#), [Central Illustration](#)) without significant regional heterogeneity.

Reductions in major bleeding with HDE compared with warfarin were observed in both regions (LatAm: HDE 2.65% vs. warfarin 3.74%; HR: 0.71; 95% CI: 0.49 to 1.03; nLAS: HDE 2.76% vs. warfarin

3.39%; HR: 0.82; 95% CI: 0.71 to 0.94) with no statistical evidence of heterogeneity by region ($p_{\text{int}} = 0.50$) ([Table 3](#), [Central Illustration](#)). The incidence of life-threatening or fatal bleeding, ICH, major or clinically relevant nonmajor bleeding, and all bleeding were significantly lower in the HDE arm compared with warfarin by a similar degree in both regions (each $p_{\text{int}} > 0.10$) ([Table 3](#)). Rates of major gastrointestinal bleeding were increased with HDE versus warfarin to a similar degree in LatAm subjects (HR: 1.33; 95% CI: 0.78 to 2.25) and nLAS (HR: 1.22; 95% CI: 0.99 to 1.50; $p_{\text{int}} = 0.77$). The primary net outcome was significantly reduced with HDE versus warfarin in both regions (HR: 0.82; 95% CI: 0.68 to 1.00, and HR: 0.91; 95% CI: 0.84 to 0.98 for LatAm subjects and nLAS, respectively; $p_{\text{int}} = 0.36$) ([Online Table 2](#)).

OUTCOMES WITH LDE VERSUS WARFARIN. When compared with warfarin, patients randomized to LDE had higher rates of ischemic stroke, but lower rates of hemorrhagic stroke and all-cause mortality ([Online Tables 3 and 4](#)).

We conducted analyses stratified by use of antiplatelet therapy at baseline (92% of which was

	Latin American												Non-Latin American											
	Warfarin (n = 888)				Higher-Dose Edoxaban (n = 886)				Higher-Dose Edoxaban vs. Warfarin				Warfarin (n = 6,148)				Higher-Dose Edoxaban (n = 6,149)				Higher-Dose Edoxaban vs. Warfarin			
	Event		Event		HR (95% CI)		p Value		Event		Event		HR (95% CI)		p Value		p _{int}							
	n	Rate (%/yr)	n	Rate (%/yr)			n	Rate (%/yr)	n	Rate (%/yr)														
Efficacy endpoints																								
Stroke/SEE	53	2.5	35	1.61	0.64 (0.42–0.99)	0.044	284	1.71	261	1.56	0.91 (0.77–1.08)	0.28	0.14											
Stroke	48	2.26	33	1.51	0.67 (0.43–1.04)	0.077	269	1.62	248	1.48	0.91 (0.77–1.09)	0.31	0.20											
Ischemic stroke	31	1.45	30	1.37	0.95 (0.57–1.56)	0.83	204	1.23	206	1.23	1.00 (0.83–1.22)	0.97	0.83											
Hemorrhagic stroke	18	0.83	3	0.14	0.16 (0.05–0.55)	0.004	72	0.43	46	0.27	0.64 (0.44–0.92)	0.016	0.037											
SEE	6	0.28	2	0.09	0.33 (0.07–1.63)	0.17	17	0.1	13	0.08	0.76 (0.37–1.57)	0.46	0.35											
Myocardial infarction	14	0.65	9	0.41	0.63 (0.27–1.46)	0.28	127	0.76	124	0.74	0.97 (0.76–1.25)	0.83	0.33											
CV hospitalization	210	10.88	168	8.43	0.77 (0.63–0.95)	0.014	1,747	12.27	1,593	10.96	0.89 (0.84–0.96)	0.001	0.19											
Death	161	7.34	144	6.47	0.88 (0.70–1.10)	0.27	678	3.97	629	3.67	0.92 (0.83–1.03)	0.16	0.70											
CV death	119	5.43	94	4.23	0.78 (0.59–1.02)	0.070	492	2.88	436	2.55	0.88 (0.78–1.00)	0.059	0.41											
Non-CV death	42	1.92	50	2.25	1.17 (0.78–1.76)	0.45	186	1.09	193	1.13	1.03 (0.84–1.26)	0.75	0.59											
CV death, stroke, SEE	145	6.81	116	5.31	0.78 (0.61–1.00)	0.047	686	4.13	612	3.66	0.88 (0.79–0.99)	0.027	0.36											
MACE*	154	7.26	123	5.66	0.78 (0.61–0.99)	0.039	772	4.69	704	4.25	0.91 (0.82–1.00)	0.056	0.25											
Safety endpoints																								
Major bleeding	67	3.74	48	2.65	0.71 (0.49–1.03)	0.074	457	3.39	370	2.76	0.82 (0.71–0.94)	0.004	0.50											
LT/fatal bleeding	32	1.76	11	0.6	0.34 (0.17–0.68)	0.002	149	1.08	83	0.61	0.56 (0.43–0.74)	<0.001	0.18											
ICH	25	1.38	6	0.33	0.24 (0.10–0.58)	0.002	107	0.78	55	0.4	0.52 (0.38–0.72)	<0.001	0.11											
Gastrointestinal	24	1.33	32	1.75	1.33 (0.78–2.25)	0.29	166	1.21	200	1.48	1.22 (0.99–1.50)	0.057	0.77											
Major or CRNM bleeding	216	13.63	166	9.98	0.74 (0.61–0.91)	0.004	1,545	12.94	1,362	11.26	0.87 (0.81–0.94)	<0.001	0.14											
Any bleeding	260	17.09	205	12.77	0.76 (0.63–0.91)	0.004	1,854	16.31	1,660	14.35	0.88 (0.83–0.94)	<0.001	0.13											
Net clinical outcomes†																								
Primary	225	10.87	190	8.9	0.82 (0.68–1.00)	0.045	1,237	7.75	1,133	7.04	0.91 (0.84–0.98)	0.016	0.36											
Secondary	183	8.53	151	6.85	0.80 (0.64–0.99)	0.043	804	4.81	733	4.35	0.90 (0.82–1.00)	0.046	0.32											
Tertiary	198	9.36	162	7.42	0.79 (0.64–0.97)	0.027	925	5.6	837	5.02	0.90 (0.82–0.98)	0.020	0.29											
Efficacy endpoints and net clinical outcomes were assessed in the intention-to-treat population including all events; safety events were assessed in the on-treatment population. See text for details. In the safety population, 885 and 884 were allocated warfarin and higher-dose edoxaban, respectively, in Latin America, while 6,127 and 6,128 were allocated warfarin and high-dose edoxaban in non-Latin America. Cox models were adjusted for dose-reduction at randomization and CHADS ₂ score (≤3 vs. <3). *Major adverse cardiovascular event, included myocardial infarction, stroke, systemic embolic event, and death due to cardiovascular causes (including bleeding). †The primary net clinical outcome was a composite of stroke, systemic embolic event, major bleeding, or death from any cause. The secondary net clinical outcome was a composite of disabling stroke, life-threatening bleeding, or death from any cause. The tertiary net clinical outcome was an exploratory composite of stroke, systemic embolic event, life-threatening bleeding, or death from any cause.																								
CHADS ₂ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack; CV = cardiovascular; HR = hazard ratio; ICH = intracranial hemorrhage; LT = life threatening; SEE = systemic embolic events.																								

aspirin) and we did not find any interaction between antiplatelet therapies and oral anticoagulants.

DISCUSSION

In this analysis comparing 2,661 subjects enrolled in LatAm centers to 18,444 enrolled elsewhere in the ENGAGE AF-TIMI 48 trial of subjects with moderate-to high-risk AF randomized to edoxaban or warfarin, we report 3 major findings:

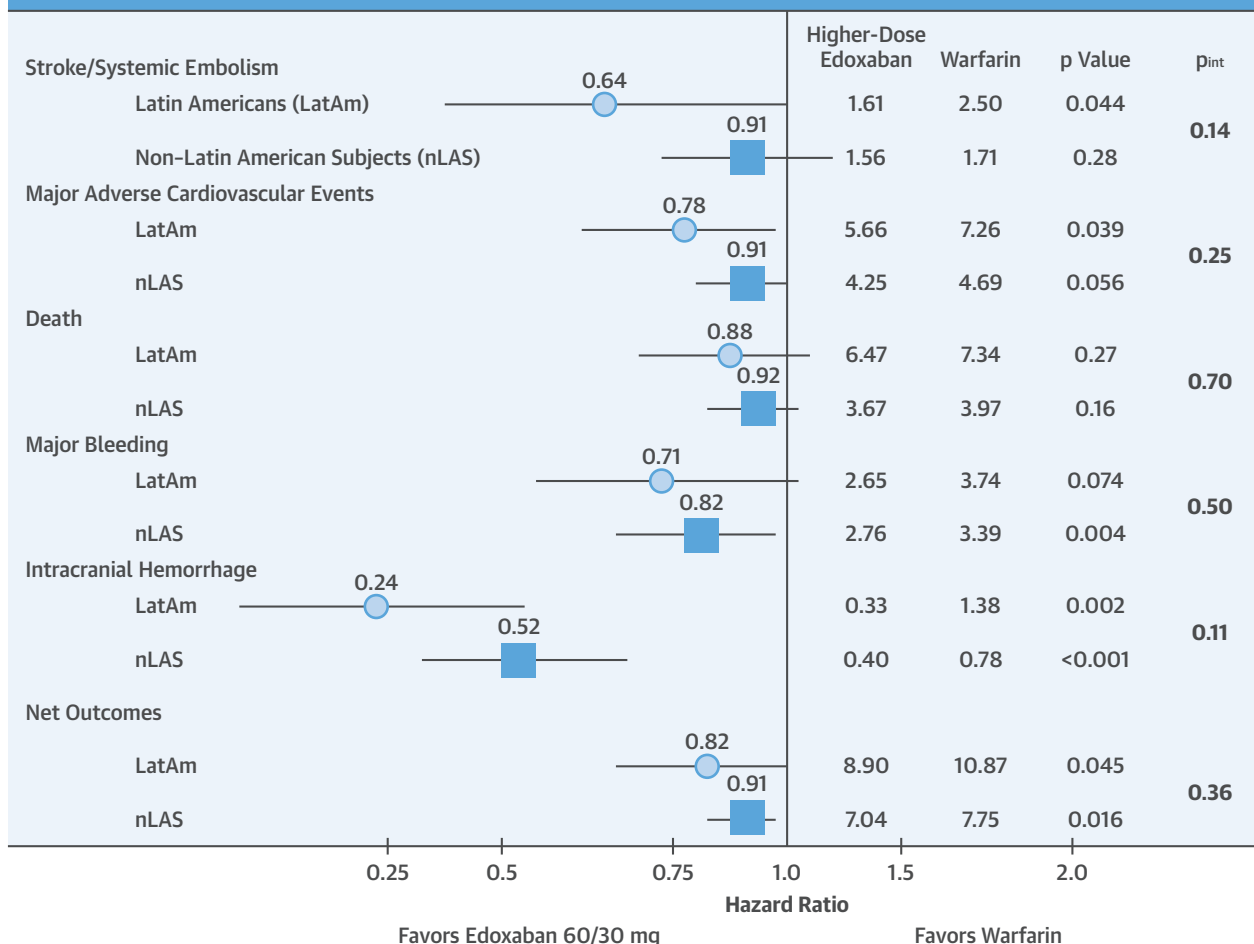
1. There were numerous differences in patient characteristics, treatments, and socioeconomic factors between regions that only partially explained higher mortality in LatAm.
2. Patients in LatAm treated with warfarin had higher rates of bleeding (particularly ICH) despite a median TTR of 66% (vs. 69% in nLAS).

3. The approved edoxaban regimen (60/30 mg once daily) significantly reduced stroke/SEE, ICH, MACE, and net outcomes compared with warfarin in LatAm, with an even greater reduction in hemorrhagic stroke in LatAm compared with areas outside of LatAm.

DIFFERENCES IN RISK PROFILES, TREATMENTS, AND MORTALITY OUTCOMES. We found significantly higher mortality rates, including both CV and non-CV death, among LatAm subjects. Although many regional differences in risk factors were present, these were not unidirectional, the absolute difference in risk scores (CHADS₂, CHA₂DS₂-VASc, Charlson Comorbidity Index) were small, and the higher mortality rates in LatAm persisted despite multivariate adjustment for baseline characteristics.

CENTRAL ILLUSTRATION Efficacy and Safety Outcomes Stratified By Treatment and Region

Higher-Dose Edoxaban Regimen vs. Warfarin in Latin America vs. Non-Latin America



Corbalán, R. et al. J Am Coll Cardiol. 2018;72(13):1466-75.

Key efficacy and safety events in subjects randomized to higher-dose edoxaban versus warfarin, stratified by region (Latin America and non-Latin America). LatAm, Latin American; nLAS, non-Latin American subjects.

There was a >2-fold difference in mean gross national index between regions that may have influenced access to care, and this contributed to the modestly lower HDI in LatAm. An exploration of the potential effect of baseline therapies revealed that nonuse of lipid-lowering drugs in LatAm was associated with an increase in CV mortality, although we cannot definitively establish a causal relationship given the lack of randomization to nonanticoagulant therapies and the possibility that lipid therapy prescription was confounded by other unmeasured factors.

Sudden death and death due to heart failure were the most frequent causes of CV deaths in the ENGAGE AF-TIMI 48 trial (11), an observation that was also reported in the GARFIELD (Global Anticoagulant Registry in the Field) AF registry of 17,116 subjects enrolled in 35 countries (12). Older subjects and those with a history of permanent AF, previous CHF, lower left ventricular ejection fraction, and reduced creatinine clearance were more likely to die of sudden death or heart failure; each of these characteristics was significantly more prevalent among LatAm

subjects. As previously reported in an observational study of urban LatAm populations (13), patients enrolled in Latin American centers in ENGAGE AF-TIMI 48 were treated less frequently with evidence-based therapies (e.g., beta-blockers, lipid-lowering therapy), while several medications not associated with mortality reduction (e.g., digoxin, amiodarone) were administered more often. Each of these factors may have contributed to the higher rate of CV death in LatAm. These findings are consistent with a recent report of the ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), where it was also observed that LatAm AF patients had higher mortality rates (14).

ORAL ANTICOAGULANTS AND OUTCOMES. In the warfarin arm, we observed higher adjusted risks of stroke/SEE, ICH, and life-threatening or fatal bleeding in LatAm subjects in addition to higher mortality rates. A limited number of studies have addressed the efficacy and safety of VKAs in LatAm subjects; these have shown high rates of stroke in association with poor INR control (15-17). Although the median TTR was lower in LatAm than nLAS, and LatAm subjects spent a greater proportion of time with an INR >3.0 (13% vs. 11%), the median TTR of 66% in LatAm was at least as high as that reported in other contemporary AF trials, and the difference between regions was small (3%); thus, differences in warfarin management do not appear to fully explain these results. Furthermore, interruption rates of study anticoagulant were significantly lower among LatAm subjects. The role of other unmeasured factors (e.g., use of complementary medical therapies affecting the response to warfarin, access, and quality of care during hospitalizations) were not ascertained in this study.

In this context of higher rates of CV and non-CV mortality observed in LatAm subjects, the use of higher-dose edoxaban, when compared to warfarin, was associated with significantly lower rates of stroke/SEE, ICH, the net primary outcome, and a 22% reduction in MACE in LatAm. The benefit of HDE relative to warfarin in reducing hemorrhagic stroke was even greater in LatAm than in nLAS; this may have been related in part to the high rate of hemorrhagic stroke among LatAm subjects treated with warfarin.

The incidences of major bleeding events, ICH, and the composite of life-threatening or fatal bleeding events were also less frequent in the HDE

arm compared to warfarin. Similar results also were reported by Yamashita *et al.* (18) in East Asian subjects in whom edoxaban significantly reduced major bleeding compared with warfarin. In the ARISTOTLE (Apixaban for Reduction of Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial with apixaban, it was found that ICH was more frequent among Asian and Latin American patients, which is consistent with our findings (19). Giugliano *et al.* (20) reported that the reduction of mortality observed with edoxaban in the ENGAGE AF-TIMI 48 trial was largely due to the significant reduction of serious bleeding events. Although LDE reduced bleeding even further, this occurs at a loss of efficacy (primarily an increase in ischemic stroke compared to warfarin); hence, clinicians are strongly advised to use 60 mg edoxaban unless 1 of the 3 specified criteria for dose reduction are present, in which case 30 mg is the recommended dose.

Thus, in Latin America, where bleeding and mortality rates were high in patients treated with warfarin, HDE represents an attractive alternative anticoagulant for patients with AF to reduce morbidity and mortality. This study confirms the benefits observed with edoxaban and the other direct oral anticoagulants (DOACs) in AF patients. This is particularly relevant in the Latin American population, where there is evidence of difficulties in achieving adequate INR control with VKAs (15). This has moved different authors to advocate for better stroke prevention strategies with DOACs in LatAm, which is also justified by cost-effectiveness studies that compared DOACs with VKAs (21-23).

STUDY LIMITATIONS. The ENGAGE AF-TIMI 48 trial was not designed or powered to explore regional differences or other subgroups. Accordingly, the data can only be considered as exploratory and hypothesis-generating. The differences in regional outcomes may be attributed to residual confounding related to differences in risk factors, warfarin management, or other unmeasured factors. Other limitations include the small sample of subjects in some countries and low event rates, which may result in type II error. Finally, results from subjects enrolled in selected centers participating in a randomized clinical trial may be different from general practice or be representative of hospitals in any 1 country or region.

CONCLUSIONS

LatAm subjects with AF had higher rates of intracranial hemorrhage and death than nLAS after

multivariable adjustment. Although event rates were higher in LatAm, outcomes with higher-dose edoxaban versus warfarin were at least as favorable in LatAm subjects as in nLAS, with an even greater reduction in hemorrhagic stroke seen in LatAm. Edoxaban represents an attractive alternative to warfarin in LatAm patients with AF to prevent major morbidity and mortality related to arterial thromboembolism and anticoagulant-related bleeding.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL

SKILLS: Regional variation in patient outcomes is multifactorial and related to demographics, comorbidities, treatment patterns, socioeconomics, and culture. In a large, international randomized trial, patients in Latin America with AF had higher rates of ICH and death than those in other regions. Compared with warfarin, treatment with edoxaban was associated with an even greater reduction in hemorrhagic stroke in Latin America than in the global trial population.

TRANSLATIONAL OUTLOOK: Additional studies of newer anticoagulants are needed to define optimal therapy for high-risk patients with AF in various settings of care.

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KEY WORDS anticoagulation, atrial fibrillation, edoxaban, Latin America

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