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Valvular Heart Disease Patients on Edoxaban or Warfarin in the ENGAGE AF-TIMI 48 Trial

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ABSTRACT

BACKGROUND The use of non-vitamin K antagonist oral anticoagulants (NOACs) instead of vitamin K antagonists (VKAs) in patients with atrial fibrillation (AF) and coexisting valvular heart disease (VHD) is of substantial interest.

OBJECTIVES This study explored outcomes in patients with AF with and without VHD in the ENGAGE AF-TIMI 48 (Effective Anticoagulation with factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48) trial, comparing edoxaban with warfarin.

METHODS Valvular heart disease was defined as history or baseline echocardiography evidence of at least moderate aortic/mitral regurgitation, aortic stenosis, or prior valve surgery (bioprosthesis replacement, valve repair, valvuloplasty). Patients with moderate to severe mitral stenosis or mechanical heart valves were excluded from the trial. Comparisons were made of rates of stroke/systemic embolic event (SSEE), major bleeding, additional efficacy and safety outcomes, as well as net clinical outcomes, in patients with or without VHD treated with edoxaban or warfarin, using adjusted Cox proportional hazards.

RESULTS After adjustment for multiple baseline characteristics, compared with no-VHD patients (n = 18,222), VHD patients (n = 2,824) had a similar rate of SSEE but higher rates of death (hazard ratio [HR]: 1.40; 95% confidence interval [CI]:1.26 to 1.56; p <0.001), major adverse cardiovascular events (HR: 1.29; 95% CI: 1.16 to 1.43; p <0.001), and major bleeding (HR: 1.21; 95% CI: 1.03 to 1.42; p = 0.02). Higher-dose edoxaban regimen had efficacy similar to warfarin in the presence of VHD (for SSEE, HR: 0.69; 95% CI: 0.44 to 1.07, in patients with VHD, and HR: 0.91; 95% CI: 0.77 to 1.07, in patients without VHD; p interaction [p_{int}] = 0.26; and for less major bleeding, HR: 0.74; 95% CI: 0.53 to 1.02 in patients with VHD, and HR: 0.82; 95% CI: 0.71 to 0.94, in patients with no VHD; p_{int} = 0.57).

CONCLUSIONS The presence of VHD increased the risk of death, major adverse cardiovascular events, and major bleeding but did not affect the relative efficacy or safety of higher-dose edoxaban versus warfarin in AF. (Global Study to Assess the Safety and Effectiveness of Edoxaban (DU-176b) vs. Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation [ENGAGE AF-TIMI 48]; NCT00781391) (J Am Coll Cardiol 2017;69:1372–82)

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Valvular heart disease (VHD) and atrial fibrillation (AF) are common conditions (1–4) and often coexist, especially in the elderly (5). Both VHD and AF are independent causes of mortality and morbidity, including a heightened risk of stroke and other thromboembolic events (2,4). Even after adjusting for other relevant concomitant conditions, VHD is associated with a 1.8- to 3.4-fold higher risk of AF in men and women, respectively (6). Risk factors for both conditions include advanced age, hypertension, diabetes, coronary heart disease, and heart failure. Valvular heart disease may be associated with an increased incidence of AF because of enlargement of the left atrium (7).

Vitamin K antagonists (VKAs) were, for many years, the mainstay of thromboprophylaxis in AF (8–10). The availability of non-VKA oral anticoagulants (NOACs) since 2009 has increased the number of AF patients treated with anticoagulants for stroke prevention (11). There is, however, uncertainty over antithrombotic prophylaxis in patients with coexisting VHD and AF, a condition often referred to as "valvular AF," but that is poorly defined by clinicians and investigators (5,12). All of the pivotal trials comparing VKAs with the NOACs in AF (13–16) have excluded patients with AF in the setting of moderate or severe mitral stenosis or with mechanical prosthetic valves, a group considered at particularly high risk of thromboembolism. To varying degrees, however, these studies included patients with other forms of VHD. It has been hypothesized that the pathogenesis of thromboembolism in patients with AF and VHD differs from those with AF without VHD and that NOACs may not provide sufficient protection from thromboembolism only in the former because of their specificity in inhibiting a single coagulation factor (5).

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We report rates of stroke/systemic embolic event (SSEE), major bleeding, and net clinical outcomes in patients with and without VHD enrolled in the ENGAGE AF-TIMI 48 (Effective Anticoagulation with factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48) trial, which compared edoxaban with warfarin.

METHODS

PATIENT POPULATION. ENGAGE AF-TIMI 48 was a randomized, double-blind, double-dummy trial comparing 2 once-daily regimens of edoxaban with warfarin in 21,105 patients with moderate-to-high-risk AF, over a median follow-up of 2.8 years. Details of the study design and trial results have been reported previously (16,17).

The primary efficacy endpoint was the time to first occurrence of total stroke or systemic embolic event (SSEE). The principal safety endpoint was International Society on Thrombosis and Haemostasis major bleeding (18).

Patients with moderate or severe mitral stenosis, a mechanical heart valve, increased risk of bleeding, severe renal failure, need for dual antiplatelet therapy, or other indication for anticoagulation therapy were excluded.

Patients were randomly allocated to a higher-dose edoxaban regimen (HDER: 60 mg once daily, adjusted to 30 mg for patients with ≥1 of the following criteria: creatinine clearance 30-49 to ml/min, weight ≤60 kg, or concomitant therapy with strong P-glycoprotein inhibitors), a lower-dose edoxaban regimen (LDER: 30 mg once daily, adjusted to 15 mg in patients with ≥1 of the previous criteria), or warfarin titrated to an international normalized ratio of 2.0 to 3.0. Eligibility criteria included electrocardiographic documentation of AF within 12 months and a $CHADS_2$ (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Prior stroke, transient ischemic attack [TIA], or thromboembolism) score ≥2. All patients provided written informed consent. Both of the once-daily regimens of edoxaban were found to be noninferior to well-managed warfarin regimens (median time-in-therapeutic range 68.4%) with respect to the prevention of total SSEE and were associated with significantly lower rates of bleeding and death from cardiovascular causes, compared with warfarin.

Patients were considered to have VHD if they had prior echocardiographic evidence of at least moderate aortic/mitral regurgitation, aortic stenosis,

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
HR_{adj} = adjusted hazard ratio
ISSEE = ischemic stroke/systemic embolic event
NOAC = non-vitamin K antagonist oral anticoagulant
p_{int} = p for interaction
SEE = systemic embolic event
SSEE = stroke/systemic embolic event
VHD = valvular heart disease
VKA = vitamin K antagonist

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prior valve repair or valvuloplasty, or prior bioprosthetic replacement of the aortic or mitral valve at baseline. All data regarding VHD were investigator reported.

OBJECTIVES. The goals of this analysis were to describe the frequency and characteristics of VHD patients in the trial population; to compare efficacy and safety outcomes of patients with or without VHD in the trial; and to assess the existence of any interaction for efficacy and safety outcomes between randomized treatment assignment and the presence or subtypes of VHD.

Because the LDER was not submitted for regulatory approval (16), data comparing the LDER with warfarin regimen are shown in the Online Appendix.

CLINICAL OUTCOMES. As in the pre-specified primary endpoint of the main trial (16,17), we report data for total SSEE. In addition, we report the data for the composite of ischemic stroke/SEE (ISSEE), most relevant for the efficacy evaluation of VHD in the Online Appendix. The principal safety endpoint, International Society on Thrombosis and Haemostasis major bleeding, other secondary efficacy endpoints, including disabling stroke (defined by means of the Rankin scores of 0 to 2 defining a nondisabling stroke, 3 to 5 a disabling stroke, and 6 a fatal stroke), other safety endpoints, and the net clinical outcomes combining efficacy and safety were as defined in the main trial (16,17). All efficacy and safety outcome events were adjudicated by an independent clinical events committee, blinded to randomized treatment assignment, using pre-specified criteria.

STATISTICAL METHODS. Continuous variables are medians with 25th and 75th percentiles, and categorical variables are numbers, percentages, and standard deviations. Continuous variables were compared using the Kruskal-Wallis test and categorical variables by the Pearson chi-square test. Kaplan-Meier event rate curves described the primary efficacy and safety outcomes by VHD status and randomized treatment.

All efficacy and net outcome analyses were performed in the intention-to-treat population and included first events after randomization, whether on or off study drug. Bleeding events were analyzed in the safety population (all patients who took at least 1 dose of the study drug) during the on-treatment time period (+3 days after the last dose in the case of premature interruption), as defined in the main trial (16,17). Hazard ratios (HRs) with 95% confidence intervals (CIs) comparing the relative efficacy and safety of edoxaban versus that of warfarin for the subgroups were calculated using the Cox proportional hazards models with treatment as a covariate, along with the following baseline characteristics: age, sex, body mass index, quartiles of creatinine, history of hypertension, history of dyslipidemia, history of diabetes, history of smoking, history of stroke or transient ischemic attack, history of heart failure, type of AF, race, region, history of increased risk of falling, history of neuropsychiatric disease, history of coronary heart disease, history of hepatic disease, history of nonintracranial hemorrhage, alcohol intake, and medications. Models were also constructed that evaluated the interaction between randomized treatment groups and VHD. Proportional hazards assumptions were assessed for VHD status and for randomized treatment by plotting Schoenfeld residuals and assessing correlation over time; no violations were suggested. Among the patients with VHD, we evaluated treatment interactions with different subtypes of VHD for the primary efficacy and safety outcomes. Analyses were performed using Stata Release version 14 (StataCorp LP, College Station, Texas) and SAS version 9.2 (SAS Institute Inc., Cary, North Carolina) software.

RESULTS

CHARACTERISTICS OF VHD PATIENTS AND PATIENT DISPOSITION. Of the 21,105 patients enrolled in ENGAGE AF-TIMI 48, 59 were excluded from the analysis because no data were provided regarding a history of VHD. Among the 21,046 remaining patients, 2,824 (13%) had a history of moderate or severe VHD (as determined by the local investigator) or had undergone prior valve surgery, and 18,222 (87%) had no VHD. These 21,046 patients, divided into VHD and no-VHD patients, were considered for the outcome analyses.

VHD and no-VHD patients were equally distributed among the randomized treatment groups, as shown in Online Table 1. The majority of patients with VHD had mitral regurgitation (10.7% of all patients enrolled), 1.7% had aortic regurgitation, 0.8% had aortic stenosis; 1.5% had prior valve surgery, and 0.9% had a bioprosthesis (**Table 1**). Categories herein are not mutually exclusive, as some patients had multiple features of valvular disease.

BASELINE CHARACTERISTICS. **Table 2** shows the baseline characteristics of the patients with VHD. These patients were slightly older, more frequently female, and had a history of heart failure; they were more likely to have persistent or permanent AF and had higher CHA_2DS_2VASc (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Prior stroke, transient ischemic attack [TIA], or

TABLE 1 Types and Frequency of VHD Patients in ENGAGE AF-TIMI 48

Category*	n	%
Mitral regurgitation	2,250	10.7
Aortic regurgitation	369	1.7
Aortic stenosis	165	0.8
Valve surgery	325	1.5
Bioprosthetic valves	191	0.9
Valve repair	123	0.6
Valvuloplasty	19	0.9

*Categories are not mutually exclusive, as 1 patient might have had multiple valve diseases.

ENGAGE AF-TIMI 48 = Effective Anticoagulation with factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 study; VHD = valvular heart disease.

thromboembolism, Vascular disease, Age 65-74 years, Sex category [female]) and HAS-BLED (Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INRs, Elderly) scores than the no-VHD patients. Additional information is provided in Online Table 1.

Among patients with and without VHD, those randomly assigned to either edoxaban or warfarin had similar baseline characteristics ($p > 0.05$ for all) (Online Table 1).

ENDPOINTS ACCORDING TO VHD STATUS. Although patients with VHD had rates of total SSEE (1.79%/year) and ISSEE (1.51%/year) that were not significantly different from patients without VHD (1.80/year and 1.52%/year, respectively; adjusted HR [HR_{adj}]: 0.9; 95% CI: 0.78 to 1.14; $p = 0.56$; and HR_{adj}: 0.93; 95% CI: 0.76 to 1.14; $p = 0.47$, respectively), they experienced other events included in the efficacy analysis more frequently. In patients with VHD, myocardial infarction (1.06%/year vs. 0.74%/year, respectively; HR_{adj}: 1.29; 95% CI: 1.00 to 1.67; $p = 0.047$), cardiovascular death (4.46%/year vs. 2.62%/year, respectively; HR_{adj}: 1.47; 95% CI: 1.30 to 1.66; $p < 0.001$), and total death (5.98%/year vs. 3.73%/year, respectively; HR_{adj}: 1.40; 95% CI: 1.26 to 1.56; $p < 0.001$) were more frequent than in patients without VHD (**Table 3**).

Major bleeding (3.16%/year vs. 2.5%/year, respectively; HR_{adj}: 1.21; 95% CI: 1.03 to 1.42; $p = 0.020$) and several secondary types of bleeding, including gastrointestinal bleeding (1.55%/year vs. 1.12%/year, respectively; HR_{adj}: 1.24; 95% CI: 0.99 to 1.56; $p = 0.065$), were numerically more frequent in patients with VHD than in patients without VHD (**Table 4**). All 3 combined measures of efficacy and safety (primary, secondary, and tertiary net clinical outcomes) occurred more frequently in VHD than in non-VHD patients (**Table 4**).

TABLE 2 Baseline Characteristics of Patients According to Treatment and Presence or Absence of VHD in ENGAGE AF-TIMI 48

	VHD (n = 2,824)	No VHD (n = 18,222)	p Value*
Age, yrs	71.8 ± 9.4	70.4 ± 9.4	<0.001
Sex, %			
Females	1,193 (42.2)	6,828 (37.5)	<0.001
Males	1,631 (57.8)	11,394 (62.5)	
BMI, kg/m^2	28.8 ± 5.7	29.6 ± 6.0	<0.001
Race, %			
White	2,382 (84.3)	14,631 (80.3)	<0.001
Asian	307 (10.9)	2,598 (14.3)	
Black	37 (1.3)	240 (1.3)	
All others	98 (3.5)	752 (4.1)	
Regions, %			
North America	745 (26.4)	3,927 (21.6)	<0.001
Latin America	221 (7.8)	2,432 (13.3)	
Western Europe	336 (11.9)	2,872 (15.8)	
Eastern Europe	1,175 (41.6)	5,960 (32.7)	
Asia-Pacific and South Africa	347 (12.3)	3,031 (16.6)	
Aspirin use at randomization, %			
No	1,990 (70.5)	1,2884 (70.7)	0.783
Yes	834 (29.5)	5,334 (29.3)	
Type of atrial fibrillation, %			
Paroxysmal	555 (19.7)	4,800 (26.4)	<0.001
Persistent	681 (24.1)	4,173 (22.9)	
Permanent	1,588 (56.2)	9,243 (50.7)	
History of coronary artery disease, %			
No	1,700 (60.2)	1,2339 (67.7)	<0.001
Yes	1,122 (39.8)	5,882 (32.3)	
History of carotid disease, %			
No	2,609 (92.4)	17,138 (94.1)	<0.001
Yes	215 (7.6)	1,077 (5.9)	
History of CHF, %			
No	742 (26.3)	8,211 (45.1)	<0.001
Yes	2082 (73.7)	10,011 (54.9)	
History of diabetes, %			
No	1,916 (67.8)	11,526 (63.3)	<0.001
Yes	908 (32.2)	6696 (36.7)	
History of hypertension, %			
No	195 (6.9)	1,154 (6.3)	0.248
Yes	2,629 (93.1)	17,068 (93.7)	
History of stroke or TIA, %			
No	2156 (76.3)	12,932 (71.0)	<0.001
Yes	668 (23.7)	5,290 (29.0)	
CrCl at randomization, ml/min	70.04 ± 29.58	77.24 ± 31.44	<0.001
$CHADS_2$ score	2.92 ± 1.00	2.83 ± 0.97	<0.001
CHA_2DS_2VASC score	4.56 ± 1.43	4.30 ± 1.38	<0.001
HAS-BLED Score	2.55 ± 0.98	2.50 ± 0.97	0.018

Values are mean ± SD or n (%). *p = chi-square test (Kruskal-Wallis for continuous variables), VHD vs. no VHD.

BMI = body mass index; CHF = congestive/chronic heart failure; CrCl = creatinine clearance; ICH = intracranial hemorrhage; TIA = transient ischemic attack; other abbreviations as in the text and Table 1.

We also explored efficacy and safety endpoints stratified by the severity of VHD, the subtypes of VHD, and the history of prior valve surgery (Online Table 2). Results in each of these subgroups are consistent with those of the overall VHD cohort, with the exception of

TABLE 3 Efficacy Outcomes by Presence or Absence of Valvular Heart Disease in ENGAGE AF-TIMI 48

ITT Cohort, Overall Study Period Primary Endpoints	VHD (n = 2,824)		No VHD (n = 18,222)		Adjusted HRs (VHD vs. no VHD)*		
	n	Event Rate (%/yr)	n	Event Rate (%/yr)	HR	95% CI	p Value†
Stroke or systemic embolic event	132	1.79	880	1.80	0.94	0.78-1.14	0.56
Ischemic stroke or systemic embolic event	112	1.51	746	1.52	0.93	0.76-1.14	0.47
Stroke	123	1.66	832	1.70	0.94	0.77-1.14	0.54
Hemorrhagic	22	0.29	147	0.30	1.07	0.67-1.70	0.79
Ischemic	103	1.39	698	1.43	0.92	0.75-1.14	0.46
Nondisabling and nonfatal	77	1.04	481	0.98	1.04	0.81-1.33	0.76
Disabling or fatal	50	0.66	372	0.75	0.84	0.62-1.13	0.24
Fatal	31	0.41	205	0.41	0.88	0.60-1.30	0.53
Systemic embolic event	9	0.12	57	0.11	0.85	0.41-1.77	0.67
Key secondary endpoints							
Stroke, systemic embolic event, or death from cardiovascular causes	424	5.72	1,920	3.92	1.31	1.17-1.46	**<0.001**
Major adverse cardiac event	472	6.44	2,182	4.50	1.29	1.16-1.43	**<0.001**
Stroke, systemic embolic event, or death	534	7.20	2,431	4.96	1.30	1.18-1.43	**<0.001**
Other endpoints							
Death or intracranial hemorrhage	477	6.35	2,024	4.08	1.38	1.24-1.53	**<0.001**
Death or disabling stroke	467	6.20	2,003	4.03	1.36	1.22-1.51	**<0.001**
Death							
Any cause	455	5.98	1,879	3.73	1.40	1.26-1.56	**<0.001**
Cardiovascular causes	339	4.46	1,318	2.62	1.47	1.30-1.66	**<0.001**
Myocardial infarction	79	1.06	363	0.74	1.29	1.00-1.67	0.047

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

CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; other abbreviations as in Table 1.

patients with aortic regurgitation and patients with prior surgery. These last 2 groups experienced event rates that did not differ significantly from patients without VHD (Online Table 2).

EFFICACT AND SAFETY OF EDOXABAN AND WARFARIN IN PATIENTS WITH AND WITHOUT VHD. The **Central Illustration** shows the Kaplan-Meier curves for total SSEE and major bleeding, respectively, by randomized treatment group and VHD status. The rates of total SSEE in patients with VHD treated with HDER versus those treated with warfarin were 1.39%/year versus 2.02%/year, respectively (HR: 0.69; 95% CI: 0.44 to 1.07); in patients without VHD, they were 1.60%/year versus 1.77%/year, respectively (HR: 0.91; 95% CI: 0.77 to 1.07; p_{int} = 0.26). In an analysis of patients receiving treatment, the corresponding results for patients with VHD treated with HDER versus warfarin were 1.00%/year versus 1.61%/year, respectively (HR: 0.60; 95% CI: 0.35 to 1.10); in patients without VHD, they were 1.21%/year versus 1.48%/year, respectively (HR: 0.82; 95% CI: 0.66 to 1.00; p_{int} = 0.25).

The rates of ISSEE in patients with VHD treated with HDER versus those treated with warfarin were 1.18%/year versus 1.65%/year, respectively; in patients without VHD, they were 1.36%/year versus 1.31%/year, respectively (p_{int} = 0.17).

The rates of major bleeding in patients with VHD treated with HDER versus those treated with warfarin were 3.28%/year versus 4.46%/year, respectively; in patients without VHD, they were 2.66%/year versus 3.27%/year, respectively (p_{int} =0.57) (Online Table 3).

Almost all treatment comparisons with respect to efficacy were consistent in patients with, versus without, VHD (**Figure 1**, Online Table 3), although all-cause death and the composite of death or disabling stroke appeared numerically to be prevented better by HDER than by warfarin in patients without VHD. Exceptions were observed for the rates of all-cause death and the rates of death or disabling stroke. In patients with VHD treated with HDER versus those treated with warfarin, the rates of death were 6.46%/year versus 5.71%/year, respectively (HR: 1.13; 95% CI: 0.90 to 1.42); in patients without VHD, they were 3.62%/year versus 4.13%/year, respectively (HR: 0.88; 95% CI: 0.78 to 0.98; p_{int} = 0.045). The rates of death or disabling stroke in patients with VHD treated with HDER versus those treated with warfarin were 6.75%/year versus 5.96%/year, respectively (HR: 1.13;

TABLE 4 Safety and Net Clinical Outcomes by Presence or Absence of VHD in ENGAGE AF-TIMI 48

Outcomes	VHD (n = 2,815)		No VHD (n = 18,152)		Adjusted HRs (VHD vs. no VHD)†		
	n	Event Rate (%/yrs)	n	Event Rate (%/yrs)	HR	95% CI	p Value§
Safety cohort*							
Major bleeding	188	3.16	1,003	2.50	1.21	1.03-1.42	**0.020**
Fatal	15	0.25	96	0.24	0.92	0.53-1.59	0.762
Bleeding into a critical organ or area	50	0.83	337	0.83	1.03	0.76-1.40	0.834
Overt bleeding with blood loss ≥2 g/dl	143	2.40	683	1.69	1.30	1.08-1.57	**0.005**
Any intracranial bleeding	28	0.46	206	0.50	0.96	0.64-1.44	0.851
Fatal intracranial bleeding	9	0.15	69	0.17	0.79	0.39-1.58	0.50
Gastrointestinal bleeding	93	1.55	455	1.12	1.24	0.99-1.56	0.065
Upper gastrointestinal tract	62	1.03	276	0.68	1.40	1.05-1.85	**0.020**
Lower gastrointestinal tract	33	0.55	186	0.46	1.04	0.71-1.54	0.83
Bleeding in other location	71	1.18	356	0.88	1.30	1.00-1.68	**0.050**
Life-threatening bleeding	26	0.43	197	0.48	0.97	0.64-1.49	0.90
Life-threatening bleeding or fatal	41	0.68	292	0.72	0.96	0.69-1.34	0.80
Clinically relevant nonmajor bleeding	528	9.68	3,050	8.27	1.13	1.03-1.24	**0.013**
Minor bleeding	257	4.46	1,591	4.13	0.98	0.86-1.13	0.82
Major or clinically relevant nonmajor bleeding	659	12.30	3,785	10.40	1.13	1.04-1.23	**0.004**
Any overt bleeding	793	15.40	4,677	13.42	1.09	1.01-1.18	**0.030**
Net clinical outcomes‡							
Primary	703	9.89	3311	6.98	1.29	1.19-1.40	**<0.001**
Secondary	498	6.66	2,194	4.44	1.34	1.21-1.49	**<0.001**
Tertiary	554	7.50	2,562	5.25	1.29	1.17-1.41	**<0.001**

*Data are from the safety cohort during the treatment period, which began when the first dose of study drug was administered, with interval censoring of events during study drug interruptions that lasted more than 3 days, except for net clinical outcomes. Data for net outcomes are presented for the overall treatment period, which began at the time of randomization and did not include interval censoring during drug interruptions. †Adjusted hazard ratios indicate adjustment for age, sex, body mass index, quartiles of creatinine, history of hypertension, history of dyslipidemia, history of diabetes, smoking, history of stroking or transient ischemic attack, history of congestive heart failure, type of atrial fibrillation, race, region, history of increased risk of falling, history of neuropsychiatric disease, history of coronary artery disease, history of hepatic disease, history of nonintracranial hemorrhage bleed, alcohol, and medications (antiplatelet agents or nonsteroidal anti-inflammatory drugs). ‡Primary = stroke, systemic embolic event, major bleeding, or any cause death. Secondary = disabling stroke, life-threatening bleeding, or any cause of death. Tertiary = stroke, systemic embolic event, life-threatening bleeding, or any cause of death. §p values in **bold** indicate statistical significance.

Abbreviations as in Table 1.

95% CI: 0.90 to 1.41); in patients without VHD, they were 3.87%/year versus 4.39%/year, respectively (HR: 0.88; 95% CI: 0.79 to 0.98; $p_{int} = 0.046$) (Online Table 3).

The main efficacy results of the ENGAGE AF-TIMI 48 trial were also consistent for the LDER when divided into VHD and no-VHD subgroups; all interaction p values were nonsignificant (Online Table 3). We also did not find significant differences in the relative safety outcomes of LDER versus warfarin (all interaction p values were nonsignificant) (**Figure 2**, Online Table 4).

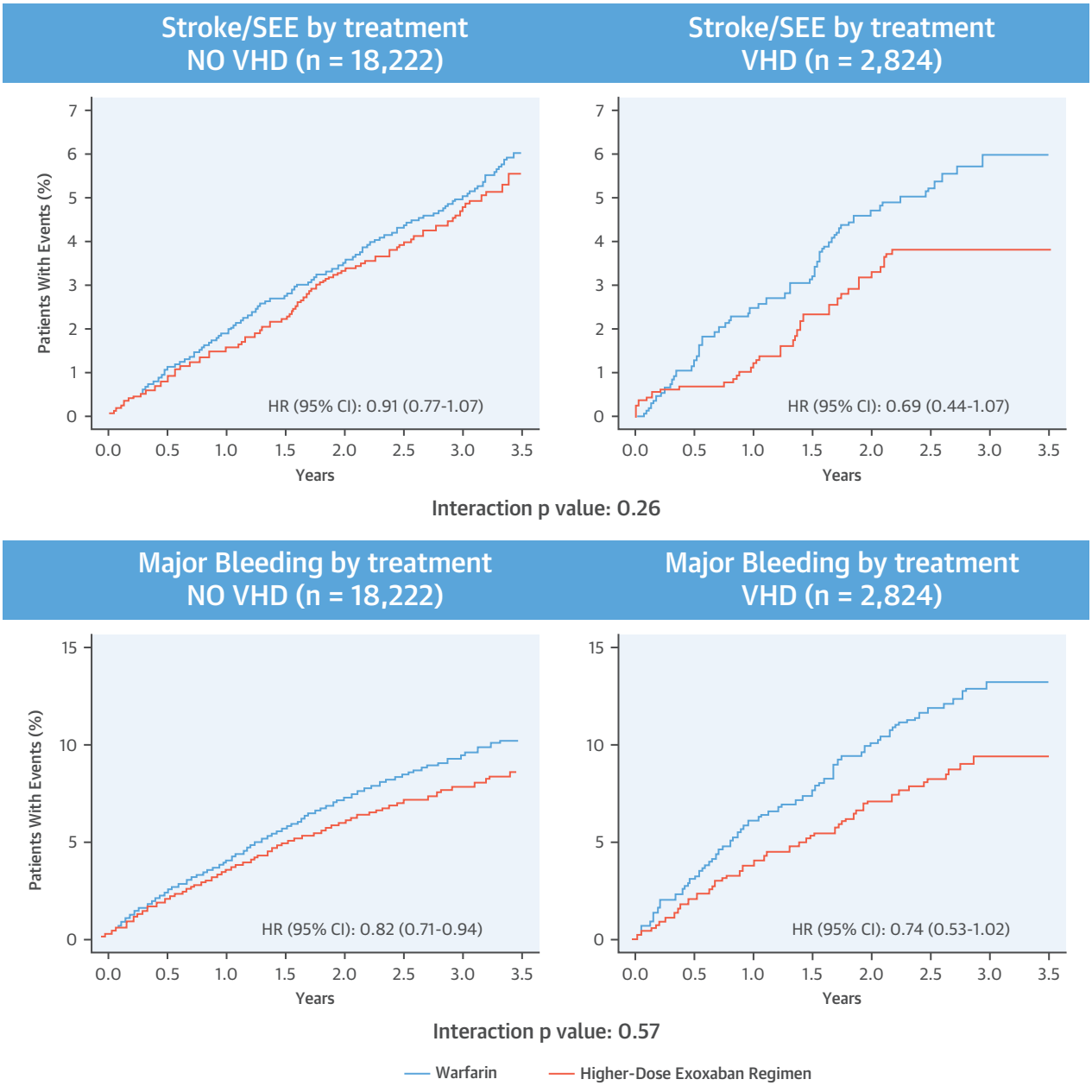
When analyzed according to valve disease location (mitral vs. aortic), prior valve surgery, and bioprosthetic valve replacement, the efficacy and safety profiles of both edoxaban dose regimens were similar regardless of the presence of the specific valvular pathology or absence of VHD.

DISCUSSION

In this analysis of patients enrolled in the ENGAGE AF-TIMI 48 trial, stratified by the presence or absence of VHD, we found that several efficacy and safety outcomes, including death, cardiovascular death, myocardial infarction, and major bleeding, were more prevalent in patients with VHD than in those without VHD, even after multivariate adjustment for differences in baseline characteristics. Nonetheless, the relative efficacy and safety of HDER compared with that of warfarin, as demonstrated in the main trial, were preserved regardless of the presence of absence of VHD. As reported in the ENGAGE AF-TIMI 48 trial (16), a variety of bleeding endpoints were significantly less frequent with edoxaban, without evidence for clinically relevant effect modification by the presence of VHD. Thus, patients with AF and VHD as included in the ENGAGE AF-TIMI 48 trial appear to derive at least the same benefit from being treated with edoxaban instead of warfarin.

The other 3 trials of a NOAC versus warfarin in patients with AF also analyzed patients with VHD. Cross-trial comparisons, however, are difficult because of differing inclusion criteria for entry into the trials, and, more importantly, marked differences

CENTRAL ILLUSTRATION **NOACs for VHD in Atrial Fibrillation: Stroke and Major Bleeding Events**

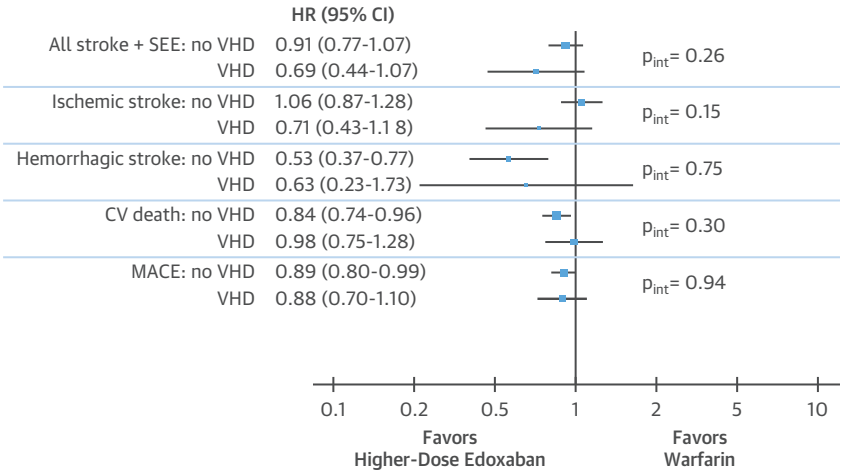


De Caterina, R. et al. J Am Coll Cardiol. 2017;69(11):1372–82.

(Top panels) Kaplan-Meier curves for total stroke or systemic embolic event by randomized treatment group and VHD status, during the study period. **(Bottom panels)** Kaplan-Meier curves for major bleeding by randomized treatment group and VHD status during the study period. NOAC = non-vitamin K antagonist oral anticoagulant; SEE = systemic embolic event; VHD = valvular heart disease.

in how VHD was defined. For example, the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) (15,19) and RE-LY (Randomized Evaluation of Long Term Anticoagulation Therapy) (13,20) trials included patients with tricuspid valve disease, which is not likely to influence arterial thromboembolic risk. The ARISTOTLE (15,19) and RE-LY (13,20) trials were also

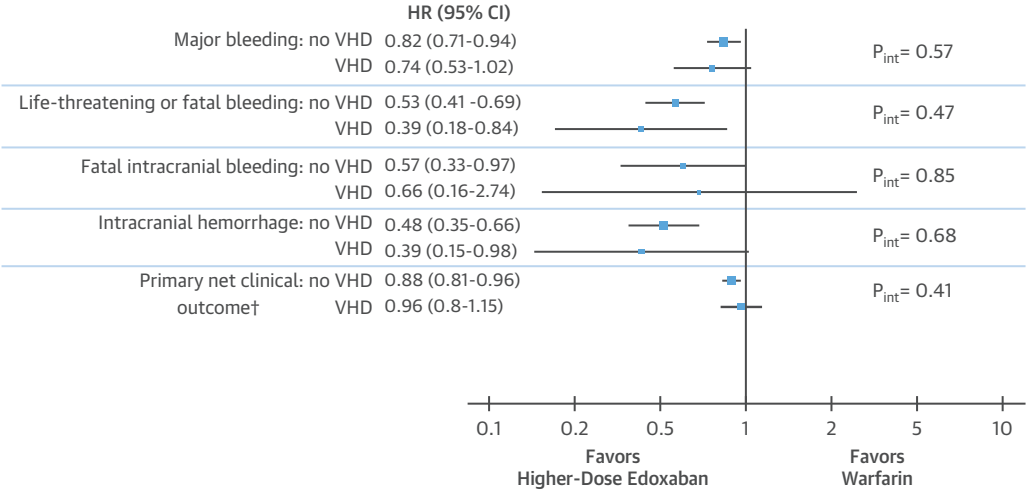
FIGURE 1 Forest Plot for Efficacy Outcomes in Patients Treated With Higher-Dose Edoxaban Versus Those Treated With Warfarin, With or Without VHD



CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MACE = major adverse cardiac event(s): defined as myocardial infarction, stroke, systemic embolic event, or death due to cardiovascular cause (including bleeding); SEE = systemic embolic event; VHD = valvular heart disease.

the only ones that included patients with mild mitral stenosis, 2 conditions not allowed in the other 2 trials. The ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism in Atrial Fibrillation) trial (14,21), while excluding patients with any type of prosthetic valves, included patients with previous annuloplasty, commissurotomy, and valvuloplasty. Nonetheless, the information from the phase-III NOAC trials is complementary, by yielding data both on the risk of VHD coexisting with AF in contemporary trials and regarding the

FIGURE 2 Forest Plot for Safety Outcomes in Patients Treated With Edoxaban Versus Those Treated With Warfarin, With or Without VHD



*Life-threatening bleeding = bleeding event that is either intracranial or associated with hemodynamic compromise requiring intervention. †Primary net clinical outcome = death from any cause, stroke, systemic embolic event, or major bleeding. Abbreviations as in Figure 1.

possibility of treating such patients with NOACs. This analysis from ENGAGE AF-TIMI 48 reports a relatively large number of patients (n = 2,824) and with the longest exposure (median follow-up: 2.8 years) for left-sided VHD patients randomized to a NOAC or warfarin therapy. The totality of evidence now indicates that patients with VHD derive similar relative benefits of NOACs compared with warfarin as do patients without VHD.

In the ENGAGE AF-TIMI 48 trial, patients with VHD were older, more frequently female, had a history of heart failure, more frequently with sustained forms of AF, and had higher CHA_2DS_2VASc and HAS-BLED scores. Most of these characteristics are associated with a higher risk of stroke and bleeding. The concomitant presence of VHD, however, significantly increased the risk (HR: 1.30) in the adjusted analysis for all composite efficacy outcomes of the trial, which included SSEE, or death from cardiovascular causes; major adverse cardiac events; and SSEE, or death. Valvular heart disease patients also had a significant adjusted increase in both major bleeding (HR_{adj}: 1.21) and gastrointestinal bleeding (HR_{adj}: 1.24) compared with patients with AF but without VHD. The reasons for these findings are unknown, not explained by the higher risk profile of the VHD subgroup, and deserve further investigation.

In ENGAGE AF-TIMI 48, the outcomes of SSEE were similar in patients with and without VHD after multivariate adjustment. The rates of death, combined efficacy outcomes, and several types of bleeding, however, were higher. The similarity of the risk of total stroke/SEE, but with higher mortality, in patients with versus those without VHD in the ENGAGE AF-TIMI 48 cohort is somewhat at variance from what was reported in the other 3 trials. In the RE-LY trial, patients with VHD had similar adjusted rates of SSEE and death and higher adjusted rates of major bleeding (20); in the ARISTOTLE trial, patients with VHD had a higher adjusted rate of SSEE, death (19); and in the ROCKET-AF trial, patients with VHD had a higher adjusted rate of SEE (21). The 4 trials are broadly in agreement on the higher risk of bleeding events in patients with VHD. The complementary information from these trials, therefore, leaves some uncertainty regarding a possibly increased risk of ischemic events in the VHD population included in the trials after adjusting for baseline variables.

If patients with AF and VHD are indeed at higher risk for ischemic events (conflicting data) and for bleeding (consistent data across the trials) than patients without VHD, patients with VHD may derive a particular benefit from oral anticoagulation therapy in general and from NOACs in particular. We did not find, however, significant major differences in the relative outcomes of edoxaban versus warfarin, with very few statistically significant treatment/VHD status interactions. The only interactions with borderline significance found in our efficacy analysis were those of treatment with overall death and for death or disabling stroke (p_{int} = 0.045 and 0.046, respectively). Although it is possible that edoxaban is more effective than warfarin in preventing death in patients without VHD, the inconsistency of these findings with those relative to other efficacy or safety endpoints in the study, the relatively low number of deaths among the smaller subgroup of patients with VHD, and the absence of adjustment for multiple testing in this exploratory analysis raise the possibility of Type I error, thus warranting caution in the interpretation. Also, the subgroup analysis whereby patients with VHD were divided according to prevailing valvular disease did not suggest a differential effects of warfarin and any of the 2 edoxaban regimens tested in ENGAGE AF-TIMI 48 for both efficacy and safety outcomes, although the number of events in some subgroups were very low. These data are therefore reassuring for the use of edoxaban in patients with VHD as defined in this trial.

Similar to the other phase-III NOAC trials, ENGAGE AF-TIMI 48 excluded patients with mechanical prosthetic valves and patients with moderate or severe mitral stenosis. The reasons for such exclusions from all NOAC trials were the higher risk of stroke under these conditions (often by far exceeding a rate of 10 stroke episodes per 100 patient-years [5]) and the need for a more intense antithrombotic regimen in patients with mechanical heart valves (22). We grouped these 2 conditions under the acronym MARM (Mechanical valve AND Rheumatic Mitral)-AF (5), with the aim of providing a clearer definition of the types of AF currently unsuitable for NOAC treatment. There is a rather cogent reason to continue to avoid NOACs in patients with mechanical prosthetic valves from stroke prevention with a NOAC given the results of the RE-ALIGN (Dabigatran Etexilate in Patients With Mechanical Heart Valves) trial, the only outcome trial with a NOAC performed in patients with mechanical heart valves. Indeed, in the RE-ALIGN trial, 2 high doses of dabigatran were associated with more strokes and more bleeding events than warfarin (23), and mechanistic data support the concept that dabigatran may be less effective than warfarin in inhibiting contact-phase-initiated coagulation (24). Conversely, there are currently no data, but also no a priori mechanistic reasons, to hypothesize a differential behavior of NOACs in AF patients

with mitral stenosis. Here the pathogenesis of thromboembolism, similar to most other forms of AF, largely involves stasis in the left atrial appendage and the left atrium, which should be preventable by NOACs (25).

STUDY LIMITATIONS. First, although pre-specified, this was a subgroup analysis of a trial powered to study a broad population with AF. Second, data presented are from a pre-specified subgroup of patients enrolled in a clinical trial with strict entry criteria. Therefore, findings may not be fully generalizable to the broader populations of patients with VHD and AF. Third, we centrally collected and centrally analyzed detailed echocardiographic information on VHD severity in only a small proportion of patients (26). Thus, classification of the type of valvular lesion for this analysis relied entirely on clinical data as reported by the local investigators. Fourth, although this study included a substantial number of patients with AF and VHD, the low event rates of many endpoints resulted in limited statistical power to detect heterogeneity in the effects of edoxaban versus warfarin. Finally, patients with versus without VHD had substantial differences in baseline characteristics, and although we used multivariable adjustment, some residual confounding likely still exists.

IMPLICATIONS AND FUTURE DIRECTIONS. The lack of homogeneity in the inclusion criteria of 4 contemporary phase III trials in defining nonvalvular AF indicates a need for a clearer and unequivocal definition of such a condition with clinical applicability. With the exception of mechanical valves and moderate-to-severe mitral stenosis (MARM-AF), it appears that NOACs could be given to many patients with VHD and coexisting AF.

Future studies should target patients with recent bioprosthetic valves and valve repair (particularly those involving annuloplasty rings), as well as populations that were excluded from the 4 phase-III trials comparing NOAC with warfarin. Additional studies are also warranted in the increasingly prevalent setting of transcatheter aortic valve implantation, as well as in moderate-to-severe mitral stenosis. A cautious approach in patients with mechanical heart valves (perhaps in patients with valves requiring less intensive anticoagulation such as the On-X [On-X Life Technologies, Kennesaw, Georgia] in the aortic position) (27), and beginning with a pharmacokinetic/pharmacodynamic study to identify the optimal dose of a factor Xa inhibitor, could pave the way to evaluate NOACs in phase III trials of patients with mechanical valves.

CONCLUSIONS

In a large contemporary clinical trial in patients with AF and an indication for oral anticoagulation, the coexistence of a history of moderate-or-severe left-sided VHD (other than mechanical valves or moderate-to-severe mitral stenosis) or prior valvular surgery is frequent and is associated with a higher risk of death, major adverse cardiovascular events, and bleeding. There was no strong evidence, however, of a differential effect in the relative efficacy of edoxaban versus warfarin in such patients for total SSEE, ISSE (which were similar between higher-dose edoxaban and warfarin), or bleeding (less frequent with edoxaban).

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with atrial fibrillation who have moderate-to-severe valvular heart disease other than mitral stenosis or mechanical heart valves, high-dose edoxaban has efficacy similar to that of warfarin and better safety. Edoxaban and other NOACs can be used in patients with atrial fibrillation and nonrheumatic native valve disease or who have undergone remote valve replacement with a bioprosthesis or valve repair.

TRANSLATIONAL OUTLOOK: The term "nonvalvular atrial fibrillation" should be abandoned in favor of more precisely specified situations in which NOACs can and cannot be used. Additional studies are needed to determine the interval after heart valve surgery beyond which NOACs can be safely prescribed.

REFERENCES

1. Soler-Soler J, Galve E. Worldwide perspective of valve disease. Heart 2000;83:721–5.

2. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet 2006;368:1005–11.

3. Iung B, Vahanian A. Epidemiology of acquired valvular heart disease. Can J Cardiol 2014;30:962–70.

4. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation 2014;129:837–47.

5. De Caterina R, Camm AJ. What is 'valvular' atrial fibrillation? A reappraisal. Eur Heart J 2014;35:3328–35.

6. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol 1998;82:2N–9N.

7. Menezes AR, Lavie CJ, DiNicolantonio JJ, et al. Atrial fibrillation in the 21st century: a current understanding of risk factors and primary prevention strategies. Mayo Clin Proc 2013;88:394–409.

8. Camm AJ, Lip GY, De Caterina R, et al. 2012 Focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 2012;33:2719–47.

9. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014;64:e1–76.

10. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893–962.

11. Kirchhof P, Ammentorp B, Darius H, et al. Management of atrial fibrillation in seven European countries after the publication of the 2010 ESC guidelines on atrial fibrillation: primary results of the PREvention oF thromboemolic events—European Registry in Atrial Fibrillation (PREFER in AF). Europace 2014;16:6–14.

12. Molteni M, Polo Friz H, Primitz L, Marano G, Boracchi P, Cimminiello C. The definition of valvular and non-valvular atrial fibrillation: results of a physicians' survey. Europace 2014;16:1720–5.

13. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139–51.

14. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883–91.

15. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981–92.

16. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093–104.

17. Ruff CT, Giugliano RP, Antman EM, et al. Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: design and rationale for the Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF–TIMI 48). Am Heart J 2010;160:635–41.

18. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692–4.

19. Avezum A, Lopes RD, Schulte PJ, et al. Apixaban in comparison with warfarin in patients with atrial fibrillation and valvular heart disease: findings from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. Circulation 2015;132:624–32.

20. Ezekowitz MD, Nagarakanti R, Noack H, et al. Comparison of dabigatran and warfarin in patients with atrial fibrillation and valvular heart disease: the RE-LY trial (Randomized Evaluation of Long-Term Anticoagulant Therapy). Circulation 2016;134:589–98.

21. Breithardt G, Baumgartner H, Berkowitz SD, et al. Clinical characteristics and outcomes with rivaroxaban vs. warfarin in patients with non-valvular atrial fibrillation but underlying native mitral and aortic valve disease participating in the ROCKET AF trial. Eur Heart J 2014;35:3377–85.

22. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012). Eur Heart J 2012;33:2451–96.

23. Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med 2013;369:1206–14.

24. Jaffer IH, Stafford AR, Fredenburgh JC, Whitlock RP, Chan NC, Weitz JI. Dabigatran is less effective than warfarin at attenuating mechanical heart valve-induced thrombin generation. J Am Heart Assoc 2015;4:e002322.

25. De Caterina R, Camm JA. Non-vitamin K antagonist oral anticoagulants in atrial fibrillation accompanying mitral stenosis: the concept for a trial. Europace 2015;18:6–11.

26. Gupta DK, Shah AM, Giugliano RP, et al. Left atrial structure and function in atrial fibrillation: ENGAGE AF–TIMI 48. Eur Heart J 2014;35:1457–65.

27. Puskas J, Gerdisch M, Nichols D, et al. Reduced anticoagulation after mechanical aortic valve replacement: interim results from the prospective randomized on-X valve anticoagulation clinical trial randomized Food and Drug Administration investigational device exemption trial. J Thorac Cardiovasc Surg 2014;147:1202–10; discussion 1210–1.

KEY WORDS anticoagulation, atrial fibrillation, edoxaban, NOACs, valvular heart disease, warfarin

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