Original Article

Stroke and Mortality Risk in Patients With Various Patterns of Atrial Fibrillation

Results From the ENGAGE AF-TIMI 48 Trial (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48)

Mark S. Link, MD; Robert P. Giugliano, MD, SM; Christian T. Ruff, MD, MPH; Benjamin M. Scirica, MD, MPH; Heikke Huikuri, MD; Ali Oto, MD; Andrea E. Crompton, RN, BSN; Sabina A. Murphy, MPH; Hans Lanz, MD; Michele F. Mercuri, MD; Elliott M. Antman, MD; Eugene Braunwald, MD; on behalf of the ENGAGE AF-TIMI 48 Investigators

Background—Whether the pattern of atrial fibrillation (AF) modifies the risk/benefit of anticoagulation is controversial. In ENGAGE AF-TIMI 48 trial (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48), the factor Xa inhibitor edoxaban was noninferior to warfarin in preventing stroke or systemic embolic events and significantly reduced bleeding and cardiovascular mortality. However, detailed analyses by AF pattern have not been reported.

Methods and Results—The 21 105 patients were categorized as having paroxysmal (<7 days duration), persistent (≥7 days but <1 year), or permanent (≥1 year or failed cardioversion) AF patterns at randomization. Efficacy and safety outcomes were evaluated during the 2.8 years median follow-up and compared by AF pattern. The primary end point of stroke/systemic embolic event was lower in those patients with paroxysmal AF (1.49%/year), compared with persistent (1.83%/year; *P*-adj =0.015) and permanent AF (1.95%/year; *P*-adj =0.004). Overall, all-cause mortality also was lower with paroxysmal (3.0%/year) compared with persistent (4.4%/year; *P*-adj <0.001) and permanent AF (4.4%/year; *P*-adj <0.001). Annualized major bleeding rates were similar across AF patterns (2.86% versus 2.65% versus 2.73%). There was no effect modification by treatment assignment.

Conclusions—In ENGAGE AF-TIMI 48 trial, patients with paroxysmal AF suffered fewer thromboembolic events and deaths compared with those with persistent and permanent AF. The efficacy and safety profile of edoxaban as compared with warfarin was consistent across the 3 patterns of AF.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00781391.

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Key Words: atrial fibrillation ■ bleeding ■ mortality ■ stroke ■ thromboembolism

Atrial fibrillation (AF) is a major cause of morbidity and mortality globally. Currently, in the United States, ≈5 million individuals have a diagnosis of AF. The American Heart Association/American College of Cardiology AF Guideline Committee estimates that the number of patients with AF will double over the next 25 years.[1] One of the major risks of AF is thromboembolism, which exists regardless of the presence or absence of symptoms.[2,3] The risk of thromboembolism for individuals with AF correlates with increases in the $CHADS_2$ and CHA_2DS_2-VASc scores.[4–7] There are conflicting data whether the pattern of AF (ie, paroxysmal, persistent, or permanent) affects the risk of thromboembolism. Thus, the current risk scoring systems do not include the pattern of AF, and American and European Guidelines recommend anticoagulation in patients at moderate or high risk, regardless of whether AF is paroxysmal, persistent, or permanent.[8–10] If the risk of thromboembolism was substantially lower in patients with paroxysmal AF, then the pattern of AF may be important to incorporate in risk scores to help guide therapeutic decisions.

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From the Department of Medicine, UTSouthwestern Medical Center, Dallas, TX (M.S.L.); TIMI Study Group, Brigham and Women's Hospital, Boston, MA (R.P.G., C.T.R., B.M.S., A.E.C., S.A.M., E.M.A., E.B.); Department of Medicine, University of Oulu, Finland (H.H.); Oulu University Hospital, Finland (H.H.); Heart and Health Foundation of Turkey, Ankara (A.O.); Daiichi-Sankyo Pharma Development, Munich, Germany (H.L.); and Daiichi-Sankyo Pharma Development, Edison, NJ (M.F.M.).

Guest Editor for this article was Gerhard Hindricks, MD.

Correspondence to Mark S. Link, MD, UTSouthwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390. E-mail mark.link@UTSouthwestern.edu

WHAT IS KNOWN

- The CHA_2DS_2-VASc score that is used to estimate the risk of stroke in atrial fibrillation (AF), does not consider the pattern of AF.
- Prior studies that attempted to assess the relation of the AF pattern to thromboembolism have shown mixed results.

WHAT THE STUDY ADDS

- In this large randomized trial of edoxaban versus warfarin, patients with paroxysmal AF suffered fewer thromboembolic events and deaths compared with those with persistent and permanent AF.
- The efficacy and safety profile of edoxaban as compared with warfarin was consistent across the 3 patterns of AF.

The ENGAGE AF-TIMI 48 trial (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48) enrolled patients with AF, without regard to whether paroxysmal, persistent, or permanent AF was present. Patients were randomized to 1 of 2 dosing regimens of once-daily edoxaban, a direct oral factor Xa inhibitor, or warfarin (target international normalized ratio, 2.0–3.0).[11] The primary results of the trial showed that both dose regimens of edoxaban were noninferior to warfarin in preventing stroke or systemic embolic events (SEEs), and both edoxaban regimens significantly reduced bleeding and cardiovascular mortality as compared with warfarin.[12] The current study is a prespecified analysis of the importance of the pattern of AF on the risks of thromboembolism, mortality, and bleeding.

Methods

Patients

Entry criteria for ENGAGE AF-TIMI 48 were previously published.[12] Briefly, the study enrolled 21 105 patients aged ≥21 years, with at least 1 episode of documented AF of any duration in the preceding 12 months, who had a $CHADS_2$ score of ≥2.[11,12] Key exclusion criteria included AF because of a reversible disorder, a creatinine clearance of <30 mL/min, a high risk of bleeding, use of dual antiplatelet therapy, moderate to severe mitral stenosis, other indications for anticoagulation, acute coronary syndrome, or coronary revascularization or stroke within 30 days. Patients were classified by the investigator as having paroxysmal (episodes of AF <7 days), persistent (duration 1 week to 1 year), or permanent (duration ≥1 year or failed electric cardioversion) AF, as defined by the AF guidelines operative at the beginning of the trial.[9] The protocol and amendments were approved by the ethics committee at each participating center. All patients provided written informed consent.

End Points

The primary efficacy end point was time to stroke (ischemic or hemorrhagic) or SEE. Secondary efficacy end points included combinations of (1) stroke, SEE, or death from cardiovascular causes, (2) all-cause mortality, (3) myocardial infarction, stroke, SEE, death from cardiovascular causes, or major bleed, and (4) stroke, SEE, or death from any cause. The principal safety end point was major bleeding as defined by the International Society on Thrombosis and Haemostasis.[13] Efficacy and net outcomes were conducted in all patients randomized counting all first events during the trial whether on or off study drug, using the intention-to-treat principle. Analyses of individual bleeding end points alone were conducted while on treatment (first dose to last dose+ days, inclusive).

Statistical Analysis

Baseline characteristics were compared across the patterns of AF using a 3-way χ^2 test. Hazard ratios (HRs) with 95% confidence intervals (CIs) comparing the relative efficacy and safety of edoxaban versus warfarin for the subgroups were calculated with the Cox proportional hazards models, with treatment as a covariate along with the stratification factors of $CHADS_2$ score and dose adjustment status. Models were also constructed that evaluated the interaction between randomized treatment group and the AF subgroup.

HRs with 95% CIs comparing the AF type were calculated using an adjusted Cox proportional hazards model, which included sex, age, race, geographic region, body mass index, smoking status, alcohol use, prior stroke or transient ischemic attack, hypertension, coronary artery disease, dyslipidemia, congestive heart failure, diabetes mellitus, increased risk of falling, hepatic disease, neuropsychiatric disease, prior non-intracranial bleed, use of antiplatelet agents at randomization, and creatinine clearance at randomization. Proportionality assumptions were assessed based on the Schoenfeld residuals for each model for type of AF, and the assumptions were not violated. Statistical correction for multiplicity was not performed for any of the tests, given the exploratory nature of the present analysis. Analyses were performed independently by the TIMI Study Group using Stata v14.1 and SAS v9.2.

Results

Baseline Findings

Of the 21 105 subjects in the ENGAGE AF-TIMI 48 trial, 5366 (25%) were classified as paroxysmal, 4868 (23%) as persistent, and 10 865 (51%) as permanent at the baseline visit prior to randomization. Patients with paroxysmal AF were similar in age (mean 70.5 years) compared with those with persistent (mean 70.2 years) and permanent (mean 70.8 years; Table 1) AF. The subjects with paroxysmal AF were more likely female and had a lower body mass index and systolic blood pressure on average. Patients with paroxysmal AF were also more likely to have a CHA_2DS_2-VASc score >3 and be treated with aspirin and amiodarone.

Outcomes

The primary outcome of stroke or SEE occurred less commonly in patients with paroxysmal AF (1.49%/year), as compared with persistent (1.83%/year; adjusted HR, 0.79; 95% CI, 0.66–0.90; P=0.015) and permanent AF (1.95%/year; adjusted HR, 0.78; 95% CI, 0.67–0.93; P=0.004; Figure 1 and Table 2). The composite secondary end point of stroke/SEE/cardiovascular death occurred less commonly in patients with paroxysmal AF (3.16%/year) compared with persistent (4.57%/year; adjusted HR, 0.77; 95% CI, 0.70–0.86; P<0.001) and permanent AF (4.49%/year; adjusted HR, 0.77; 95% CI, 0.70–0.87; P<0.001; Figure 2).

Overall mortality was lower in those with paroxysmal (2.99%/year) compared with persistent (4.41%/year; adjusted HR, 0.73; 95% CI, 0.64–0.83; P<0.001) and permanent AF (4.41%/year; adjusted HR, 0.78; 95% CI, 0.69–0.87; P<0.001; Figure 3). The composite of myocardial infarction, stroke, SEE, and death because of cardiovascular causes or bleeding was observed in 3.90%/year in subjects with paroxysmal compared with 5.09%/year in persistent (adjusted HR, 0.79; 95% CI, 0.71–0.89; P<0.001) and 5.04%/year in permanent AF (adjusted HR, 0.84; 95% CI, 0.76–0.93; P=0.001). Stroke, SEE, or death from any cause occurred in 4.08%/year of paroxysmal compared with 5.68%/year in persistent (adjusted HR, 0.75; 95% CI, 0.68–0.84; P<0.001) and 5.68%/year permanent (adjusted HR, 0.80; 95% CI, 0.72–0.88; P<0.001) AF.

Table 1. Baseline Characteristics of the Patients in ENGAGE AF-TIMI 48

	Paroxysmal, %	Persistent, %	Permanent, %	Two-Way *P* Values		
				Paroxysmal vs Persistent	Paroxysmal vs Permanent	Persistent vs Permanent
Age, y, mean (SD)	70.5 (9.5)	70.2 (9.7)	70.8 (9.2)	0.099	0.29	0.004
Age ≥65 y	73.8	72.3	74.8	0.082	0.19	0.001
Age ≥75 y	40.5	38.7	40.6	0.064	0.85	0.021
Male sex	54.7	62.5	65.2	<0.001	<0.001	0.001
Weight, kg, mean (SD)	82.8 (20.0)	84.2 (21.1)	84.3 (19.9)	<0.001	<0.001	0.48
BMI, mean (SD)	29.3 (6.0)	29.6 (6.3)	29.5 (5.8)	0.049	0.018	0.98
VKA naïve	51.5	52.7	30.6	0.24	<0.001	<0.001
$CHADS_2$ score >3	20.0	19.9	25.1	0.91	<0.001	<0.001
CHA_2DS_2-Vasc score >3	72.8	68.2	70.8	<0.001	0.010	<0.001
Prior stroke or TIA	29.0	25.0	29.4	<0.001	0.61	<0.001
Prior stroke	17.4	16.0	20.5	0.057	<0.001	<0.001
Prior TIA	13.9	10.8	10.9	<0.001	<0.001	0.86
Prior valvular disease	17.4	21.1	22.8	<0.001	<0.001	0.016
Hypertension	93.9	93.6	93.5	0.51	0.30	0.81
History of CAD	35.5	30.8	33.3	<0.001	0.007	0.001
Prior coronary revasc	14.6	13.0	11.3	0.017	<0.001	0.003
Prior CABG	7.9	7.3	6.2	0.27	<0.001	0.008
Prior PCI	8.1	6.9	6.1	0.014	<0.001	0.089
Prior MI	12.0	11.2	11.4	0.19	0.30	0.62
History of PAD	3.9	3.6	4.2	0.53	0.34	0.10
History of CHF	45.4	59.7	62.4	<0.001	<0.001	0.001
History of diabetes mellitus	37.5	36.1	35.4	0.14	0.008	0.38
Current smoker	7.3	8.0	7.1	0.18	0.55	0.032

BMI indicates body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; ENGAGE AF-TIMI 48 Trial, Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; and VKA, vitamin K antagonist.

Bleeding Events

There was no difference in annualized major bleeding rates between the groups: 2.86% in paroxysmal versus 2.65% in persistent (adjusted HR, 1.07; 95% CI, 0.92–1.21; *P*=0.42) and 2.73% in permanent (adjusted HR, 1.01; 95% CI, 0.88–1.16; *P*=0.87; Table 2) AF. The annualized rate of combined major and clinically relevant nonmajor bleeding was 12.17%/year in patients with paroxysmal AF, which tended to be higher than in patients with persistent (10.68%/year; adjusted HR, 1.08; 95% CI, 0.99–1.17; *P*=0.07) or with permanent AF (10.37%; adjusted HR, 1.08; 95% CI, 1.01–1.16; *P*=0.035).

Outcomes by Treatment and AF Pattern

There were no statistically significant interactions in the key efficacy end points when stratified by AF pattern (Table 3). Similarly, no significant interactions were observed for the major safety end points or net outcomes, which combined efficacy and safety events. The efficacy and safety profile of edoxaban as compared with warfarin was consistent across the 3 patterns of AF.

Discussion

The ENGAGE AF-TIMI 48 trial provided the opportunity to characterize the baseline features, including the pattern of AF, and response to the once-daily oral factor Xa inhibitor, edoxaban, in a prespecified analysis of 21 105 patients with nearly 60 000 patient-years of observation. Patients with paroxysmal AF were younger, more likely female, have a CHA_2DS_2-VASc score >3, and to be treated with aspirin, amiodarone, and digoxin. Patients with paroxysmal AF enrolled in this trial (all of whom had a $CHADS_2$ score of at least 2) were at substantial risk for arterial thromboembolism (1.5%/year) and death (3%/year).

Patients in ENGAGE AF-TIMI 48 with paroxysmal AF were less likely to experience thromboembolic outcomes compared with patients with persistent or permanent AF. This finding persisted after multivariable adjustment. In addition, patients with paroxysmal AF were less likely to have the combined end point of systemic embolism and cardiovascular death, and their overall all-cause mortality was lower compared with that of patients with persistent or permanent AF.

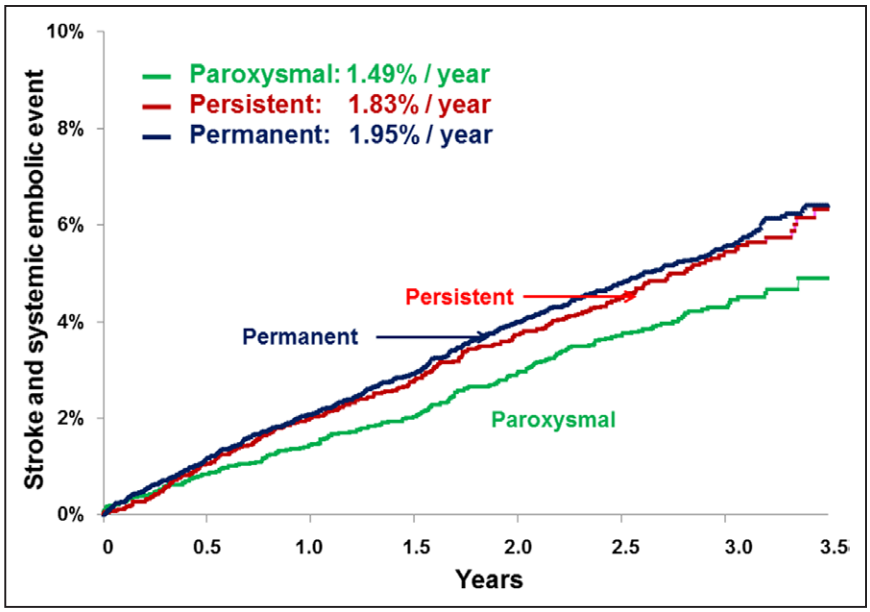

Figure 1. Stroke and systemic embolic event (SEE) occurred less frequently in the patients with paroxysmal atrial fibrillation (AF) (1.49%/y), as compared with persistent (1.83%/y; HR, 0.79; 95% CI, 0.66–0.96; *P*=0.015) and permanent AF (1.95%/y; HR, 0.79; 95% CI, 0.67–0.93; *P*=0.004) after multivariable adjustment (see Statistical Methods for covariates). CI indicates confidence interval; and HR, hazard ratio.

There was no difference in these end points between patients with persistent or permanent AF. Similarly, major bleeding did not differ by AF pattern. However, the composite of major or clinically relevant bleeding tended to be more frequent in patients with paroxysmal AF.

Prior studies have been conflicting on whether patients with paroxysmal AF have a lower risk of thromboembolism compared with those with persistent and permanent AF. Early observational data reported a lower risk of embolic events in patients with paroxysmal AF compared with permanent AF.[14–16] However, in the SPAF trial (stroke prevention in atrial fibrillation), the 460 patients with paroxysmal AF had a similar incidence of thromboembolism compared with the 1552 patients with persistent and permanent AF.[17]

Larger and more recent trials of direct anticoagulants have had conflicting results. In the SPORTIF (Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation),[18] ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation),[19] ROCKET (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation),[20] and ACTIVE-A (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events-Aspirin)/AVERROES (Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment Study),[21] patients with paroxysmal AF had a lower risk of stroke/SEE compared with persistent AF. In the RELY trial (Randomized Evaluation of Long Term Anticoagulation Therapy),[22] although the risk of stroke/SEE was lower (1.32%/year) in patients with paroxysmal AF, this was not statistically significantly different than persistent (1.55%/year) and permanent (1.49%/year) AF.

The ENGAGE AF-TIMI 48 trial, with the largest subject enrollment of any previous anticoagulation study, confirms that patients with paroxysmal AF have a lower risk of thromboembolism compared with those with nonparoxysmal AF. Despite subtle differences in the population

Table 2. Clinical Outcomes by AF Pattern of the Patients in ENGAGE AF-TIMI 48

	Event Rate, %/y			Paroxysmal vs Persistent		Paroxysmal vs Permanent		Persistent vs Permanent	
	Paroxysmal	Persistent	Permanent	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Stroke/SEE (Figure 1)	1.49	1.83	1.95	0.79 (0.66–0.96)	0.015	0.79 (0.67–0.93)	0.004	0.99 (0.85–1.16)	0.95
Stroke/SEE/CV death (Figure 2)	3.16	4.57	4.49	0.73 (0.64–0.82)	<0.001	0.78 (0.70–0.87)	<0.001	1.07 (0.97–1.18)	0.18
All-cause death (Figure 3)	2.99	4.41	4.41	0.73 (0.64–0.83)	<0.001	0.78 (0.69–0.87)	<0.001	1.06 (0.96–1.17)	0.23
Major bleeding	2.86	2.65	2.73	1.07 (0.91–1.25)	0.42	1.01 (0.88–1.16)	0.87	0.95 (0.82–1.09)	0.45
Major or clinically relevant nonmajor bleeding	12.17	10.68	10.37	1.08 (0.99–1.17)	0.070	1.08 (1.01–1.16)	0.035	1.00 (0.93–1.08)	>0.99
MACE (MI/stroke/SEE/CV death)	3.90	5.09	5.04	0.79 (0.71–0.89)	<0.001	0.84 (0.76–0.93)	0.001	1.06 (0.96–1.16)	0.23
Death/stroke/SEE	4.08	5.68	5.68	0.75 (0.68–0.84)	<0.001	0.80 (0.72–0.88)	<0.001	1.06 (0.97–1.16)	0.21

HR adjusted for sex, age, race, geographic region, BMI, smoking status, alcohol use, prior stroke or TIA, hypertension, coronary artery disease, dyslipidemia, congestive heart failure, diabetes mellitus, increased risk of falling, hepatic disease, neuropsychiatric disease, prior non-ICH bleed, use of antiplatelet agents at randomization, and creatinine clearance at randomization. AF indicates atrial fibrillation; BMI, body mass index; CI, confidence interval; CV, cardiovascular; ENGAGE AF-TIMI 48 Trial, Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48; HR, hazard ratio; MACE, myocardial infarction, all stroke, systemic embolic events, or death from cardiovascular causes; MI, myocardial infarction; SEE, systemic embolic events; and TIA, transient ischemic attack.

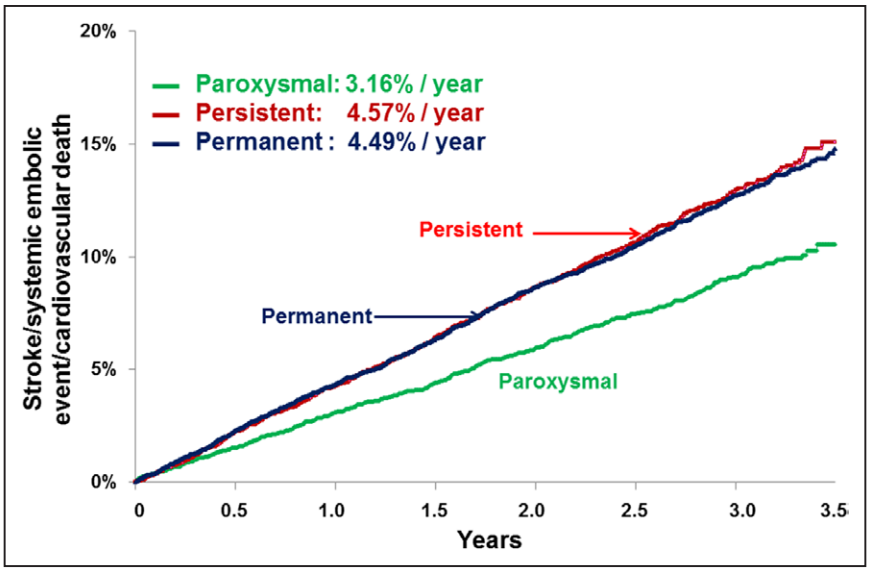

Figure 2. The composite secondary end point of stroke/SEE/cardiovascular (CV) death occurred less commonly in patients with paroxysmal atrial fibrillation (AF; 3.16%/y) compared with persistent (4.57%/y; HR, 0.73; 95% CI, 0.64–0.82; *P*<0.001) and permanent AF (4.49%/y; HR, 0.78; 95% CI, 0.70–0.87; *P*<0.001) after multivariable adjustment (see Statistical Methods for covariates). CI indicates confidence interval; HR, hazard ratio; and SEE, systemic embolic events.

studied, including the collection and analysis of patient variables, the results of ENGAGE AF-TIMI 48 trial are concordant with most of the modern anticoagulation trials. Still unresolved is whether paroxysmal AF is associated with a lower risk of thromboembolism via sharing underlying mechanisms, such as fibrosis and atrial dilatation, or indeed whether the shorter time in AF is directly implicated. In addition, patients with paroxysmal AF enrolled in the ENGAGE AF-TIMI 48 trial had a lower mortality than those with nonparoxysmal AF.

There was no strong evidence for effect modification by the pattern of AF on the relative benefit and safety of edoxaban as compared with warfarin with regard to the primary and key secondary study end points. Thus, the benefits of edoxaban seem to extend to patients with paroxysmal AF, as well as to those patients with a higher burden of AF. Specifically, the risk of stroke or SEE with edoxaban compared with warfarin was not affected by the pattern of AF, while cardiovascular death was reduced with edoxaban compared with warfarin, regardless of AF pattern. On balance, therapies such as edoxaban that reduce bleeding while preserving the efficacy observed with warfarin to prevent thromboembolic events may be particularly desirable in patients who are at lower risk of thromboembolism, such as patients with paroxysmal AF.

Limitations

Investigator determination of AF pattern is known to result in misclassification error, as highlighted in a recent study,[23] although only 2% of those clinically classified as paroxysmal AF had permanent AF. Furthermore, in this recent study, patients with paroxysmal AF had a much lower burden of AF than the other groups; thus, our clinical classification of paroxysmal AF is likely to be truly reflective of paroxysmal AF. All the patients in the current trial were deemed to be acceptable for anticoagulation. In clinical practice, not all patients are acceptable for anticoagulation, and our results may not be generalizable. In this trial, the duration of AF was not collected. Duration of AF may be an important determinant of risk of thromboembolism. In addition, the candidate variables in our models were

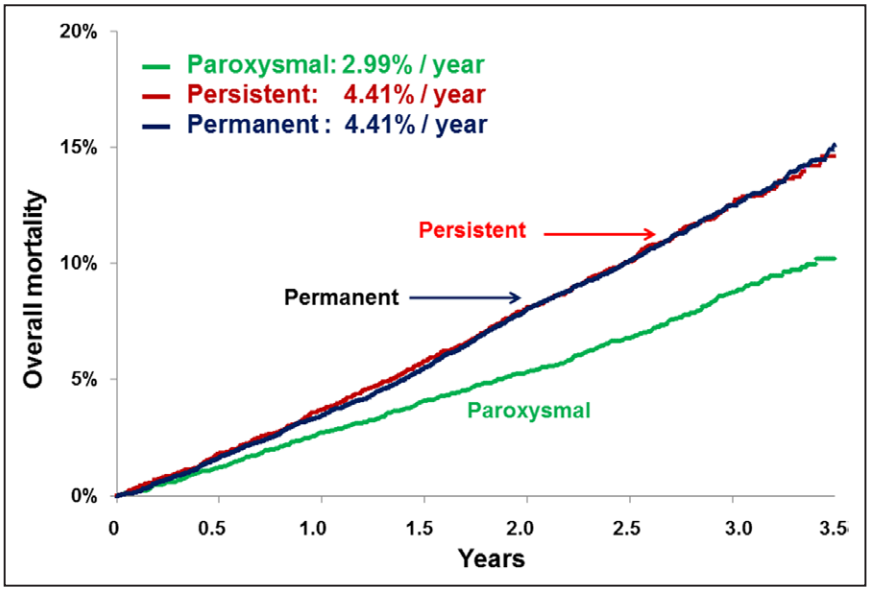

Figure 3. The end point of overall mortality was lower in those with paroxysmal (2.99%/y) compared with persistent (4.41%/y; HR, 0.73; 95% CI, 0.64–0.83; *P*<0.001) and permanent atrial fibrillation (AF; 4.41%/y; HR, 0.78; 95% CI, 0.69–0.87; *P*<0.001) after multivariable adjustment (see Statistical Methods for covariates). CI indicates confidence interval; and HR, hazard ratio.

Table 3. Outcomes by Treatment Groups Stratified by AF Pattern at Randomization

	Paroxysmal AF, HR (95% CI) vs Warfarin		Persistent AF, HR (95% CI) vs Warfarin		Permanent AF, HR (95% CI) vs Warfarin		Interaction *P* Value	
	HDER	LDER	HDER	LDER	HDER	LDER	HDER	LDER
Stroke/SEE	1.26 (0.90–1.78)	1.31 (0.94–1.83)	0.82 (0.59–1.12)	0.97 (0.72–1.33)	0.77 (0.62–0.96)	1.15 (0.94–1.39)	0.050	0.43
Major bleeding	0.82 (0.64–1.04)	0.42 (0.32–0.56)	0.74 (0.56–0.97)	0.57 (0.43–0.77)	0.82 (0.69–0.98)	0.53 (0.44–0.64)	0.80	0.31
Stroke/SEE/CV death	1.01 (0.81–1.27)	0.94 (0.75–1.18)	0.81 (0.66–0.98)	0.87 (0.72–1.06)	0.84 (0.74–0.96)	0.99 (0.87–1.13)	0.29	0.55
All-cause death	0.93 (0.75–1.16)	0.78 (0.62–0.98)	0.83 (0.68–1.01)	0.84 (0.69–1.03)	0.95 (0.83–1.09)	0.92 (0.80–1.05)	0.51	0.45
MACE	1.07 (0.87–1.31)	1.01 (0.83–1.24)	0.81 (0.67–0.97)	0.90 (0.75–1.09)	0.85 (0.75–0.97)	1.00 (0.89–1.14)	0.11	0.64
Death/stroke/SEE	1.02 (0.84–1.24)	0.93 (0.76–1.13)	0.80 (0.67–0.95)	0.86 (0.72–1.02)	0.90 (0.80–1.01)	0.98 (0.87–1.10)	0.19	0.45

AF indicates atrial fibrillation; CI, confidence interval; CV, cardiovascular; HDER, higher-dose edoxaban regimen; HR, hazard ratio; LDER, lower-dose edoxaban regimen; MACE, myocardial infarction, all stroke, systemic embolic events, or death from cardiovascular causes; and SEE, systemic embolic events.

selected from the baseline characteristics that were collected, and we cannot account for unmeasured confounders.

Conclusion

In the ENGAGE AF-TIMI 48 trial, patients with paroxysmal AF suffered fewer thromboembolic events and had lower all-cause mortality compared with those with persistent and permanent AF. This effect persisted after adjustment for baseline variables. Yet, even these lower-risk patients with paroxysmal AF benefited from anticoagulation with edoxaban compared with warfarin.

Sources of Funding

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Disclosures

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Stroke and Mortality Risk in Patients With Various Patterns of Atrial Fibrillation: Results From the ENGAGE AF-TIMI 48 Trial (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48)

Mark S. Link, Robert P. Giugliano, Christian T. Ruff, Benjamin M. Scirica, Heikke Huikuri, Ali Oto, Andrea E. Crompton, Sabina A. Murphy, Hans Lanz, Michele F. Mercuri, Elliott M. Antman and Eugene Braunwald
on behalf of the ENGAGE AF-TIMI 48 Investigators

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