ORIGINAL RESEARCH

Concomitant Use of Single Antiplatelet Therapy With Edoxaban or Warfarin in Patients With Atrial Fibrillation: Analysis From the ENGAGE AF-TIMI48 Trial

Haiyan Xu, MD; Christian T. Ruff, MD, MPH; Robert P. Giugliano, MD, SM; Sabina A. Murphy, MPH; Francesco Nordio, PhD; Indravadan Patel, MD; Minggao Shi, PhD; Michele Mercuri, MD, PhD; Elliott M. Antman, MD; Eugene Braunwald, MD

***Background*—**We studied the concomitant use of single antiplatelet therapy (SAPT) on the efficacy and safety of the anti-Xa agent edoxaban in patients with atrial fibrillation (AF).

***Methods and Results*—**ENGAGE AF-TIMI 48 was a randomized trial that compared 2 dose regimens of edoxaban with warfarin. We studied both the approved high-dose edoxaban regimen (HDER; 60 mg daily reduced by one half in patients with anticipated increased drug exposure), as well as a lower-dose edoxaban regimen (LDER; 30 mg daily, also reduced by one half in patients with anticipated increased drug regimen). SAPT (aspirin in 92.5%) was administered at the discretion of the treating physician. Cox proportional hazard regressions stratified by SAPT at 3 months with treatment as a covariate were performed. The 4912 patients who received SAPT were more frequently male, with histories of coronary artery disease and diabetes, and had higher $CHADS_2Vasc$ and HAS BLED scores than did the 14 977 patients not receiving SAPT. When compared to patients not receiving SAPT, those receiving SAPT had a higher incidence of major bleeding; (adjusted hazard ratio [HR_{adj}]=1.46; 95% CI, 1.27–1.67, $P<0.001$). SAPT did not alter the relative efficacy of edoxaban compared to warfarin in preventing stroke or systemic embolic events (SEEs): edoxaban versus warfarin without SAPT, hazard ratio (HR_{adj} for HDER)=0.94; (95% CI: 0.77–1.15) with SAPT, HR_{adj}=0.70 (95% CI: 0.50–0.98), *P* interaction (P_{int})=0.14. (HR_{adj} for LDER versus warfarin without SAPT=1.19 (95% CI 0.99–1.43) With SAPT, 1.03 (95% CI, 0.76–1.39) P_{int}=0.42. Major bleeding was lower with edoxaban than warfarin both without SAPT, HR_{adj} for HDER=0.80 (95% CI, 0.68–0.95), and with SAPT, HR_{adj}=0.82 (95% CI, 0.65–1.03; P_{int}=0.91). For LDER without SAPT (HR_{adj}=0.56 [95% CI 0.46–0.67]) and with SAPT (HR_{adj}=0.51 [95% CI 0.39–0.66]).

***Conclusions*—**Patients with AF who were selected by their physicians to receive SAPT in addition to an anticoagulant had a similar risk of stroke/SEE and higher rates of bleeding than those not receiving SAPT. Edoxaban exhibited similar relative efficacy and reduced bleeding compared to warfarin, with or without concomitant SAPT.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov/. Unique identifier: NCT00781391. **(*J Am Heart Assoc*. 2016;5: e002587 doi: 10.1161/JAHA.115.002587)**

Key Words: anticoagulant • antiplatelet • atrial fibrillation • edoxaban

As previously reported, in patients with nonvalvular atrial fibrillation (AF), the Effective aNticoaGulation with factor xA next GEneration in AF-Thrombolysis In Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial showed that the factor Xa inhibitor, edoxaban, was noninferior to warfarin in the prevention of stroke or systemic embolic event (stroke/SEE) and resulted in significantly lower rates of bleeding and cardiovascular death.[1] Patients with nonvalvular AF are frequently elderly and have a high prevalence of chronic coronary artery disease (CAD).[2,3] Though oral anticoagulants are more effective than antiplatelet agents in preventing stroke/SEE in patients with AF, it is thought that the latter

From the TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (H.X., C.T.R., R.P.G., S.A.M., F.N., E.M.A., E.B.); Daiichi Sankyo Pharma Development, Edison, NJ (I.P., M.S., M.M.).

Accompanying Tables S1 through S3 are available at http://jaha.ahajournals.org/content/5/2/e002587/suppl/DC1

Correspondence to: Eugene Braunwald, MD, TIMI Study Group, Brigham and Women's Hospital, 350 Longwood Ave, 1st office floor, Boston, MA 02115. E-mail: ebraunwald@partners.org

Received August 24, 2015; accepted January 19, 2016.

may be more protective in reducing vascular events in patients with CAD or at high risk of acute coronary events.[4,5] The choice of optimal antithrombotic management to prevent both thromboembolic and acute ischemic events in patients with AF and coexisting CAD is challenging given that combination therapy of anticoagulant and antiplatelet agents is associated with an increased risk of bleeding and its efficacy is not clear.[6–10] Here, we report on the effects of single antiplatelet therapy (SAPT) on the comparison of edoxaban with warfarin in patients with non-valvular AF.

Methods and Results

Study Population and Treatments

ENGAGE AF-TIMI 48 was a multinational, double-blind randomized trial that compared the efficacy and safety of 2 dosing regimens of edoxaban with warfarin.[1,11] The trial was approved by all institutional review committees and subjects provided informed consent. Edoxaban was provided by the sponsor, Daiichi Sankyo (Parsippany, NY), who also funded the trial. Briefly, 21 105 patients with a history of documented AF and a $CHADS_2$ score $\geq$2 were enrolled. Key exclusion criteria were severe renal dysfunction (creatinine clearance [CrCl] <30 mL/min), a high bleeding risk, receiving or anticipated to receive dual antiplatelet therapy, or a history of stroke, acute coronary syndrome, or coronary revascularization within 30 days of randomization. The trial studied 2 dose regimens of edoxaban. The higher dose edoxaban regimen (HDER) was approved by the US Food and Drug Administration and the European as well as Japanese Medicine Agencies. This dose (60 mg/day) was reduced to 30 mg/day if any of the following characteristics, which would be expected to increase drug exposure, were present at the time of randomization or occurred during the trial[12]: CrCl 30 to 50 mL/min; body weight $\leq$60 kg; or concomitant use of potent P-glycoprotein inhibitors (verapamil, quinidine, or dronedarone). The lower-dose regimen (LDER) was 30 mg/day and reduced to 15 mg/day for the same reasons. SAPT was administered as directed by the treating physician; aspirin $\leq$100 mg daily was strongly encouraged. If a clinical indication for dual antiplatelet therapy arose after randomization, the study drug was temporarily interrupted, but open-label vitamin K antagonist (VKA) was permitted. Warfarin was well managed during the trial with median time in the therapeutic range (mTTR) of 68.4%.[1]

Patients with events (death, stroke, systemic embolic event [SEE], or major bleeding) occurring before the 3 months visit were excluded from the primary analysis because a sizeable percentage of patients (n=498; 7.46%) discontinued SAPT after they entered the ENGAGE AF-TIMI 48 trial and were begun on anticoagulant therapy. Therefore, in our primary analysis we compared SAPT with no SAPT beginning 3 months after randomization. Patients with or without SAPT use at randomization were evaluated in a sensitivity analysis.

Endpoints

Endpoints were the same as those prespecified in the ENGAGE-TIMI 48 trial.[1,11,13] The primary efficacy endpoint was stroke/SEE and the primary safety endpoint was major bleeding as per the International Society on Thrombosis and Hemostasis (ISTH) criteria; the primary net clinical outcome was a composite of stroke/SEE, all-cause death, or major bleeding. Cardiovascular death, myocardial infarction (MI), intracranial hemorrhage (ICH), life -threatenig bleeding, and major plus clinically relevant nonmajor bleeding were also analyzed.[1] All end points were adjudicated by a blinded clinical endpoint committee.

Statistical Methods

Baseline characteristics across subgroups were compared using the chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables. The Cox proportional hazard method was used to calculate the hazard ratio (HR) of edoxaban to warfarin. Comparison of outcomes in patients receiving and not receiving SAPT at 3 months was performed going forward, after adjustment for the following baseline characteristics: age, sex, geographic region; weight; CrCl; smoking; CAD; previous MI; previous coronary revascularization; dyslipidemia; diabetes; peripheral arterial disease; history of carotid arterial disease; type of AF; VKA naïve. Nonlinearity in continuous covariates was handled by cubic splines. Statistical analyses were performed in SAS software (version 9.2; SAS Institute, Inc., Cary, NC). All outcomes reported were annualized.

Results

At enrollment, 7036 subjects were randomized to warfarin, 7035 to the HDER and 7034 to the LDER, respectively (Figure 1). At randomization, 6678 of the 21 105 subjects (31.6%) were receiving SAPT and 7.46% of all subjects discontinued SAPT before the 3-month visit in both the warfarin and edoxaban groups. The present analysis was carried out in 19 909 subjects, 4912 of whom (24.7%) were and 14 977 (75.3%) who were not receiving a SAPT at the 3-month visit. After the 3 month visit, the percentage of patients receiving SAPT remained between 24% and 25% during the remainder of the trial, and the present analysis is based on these 4912 patients (Table 1). Of the 4912 patients on SAPT, 4525 (92.5%) were taking aspirin, (most [92%] of

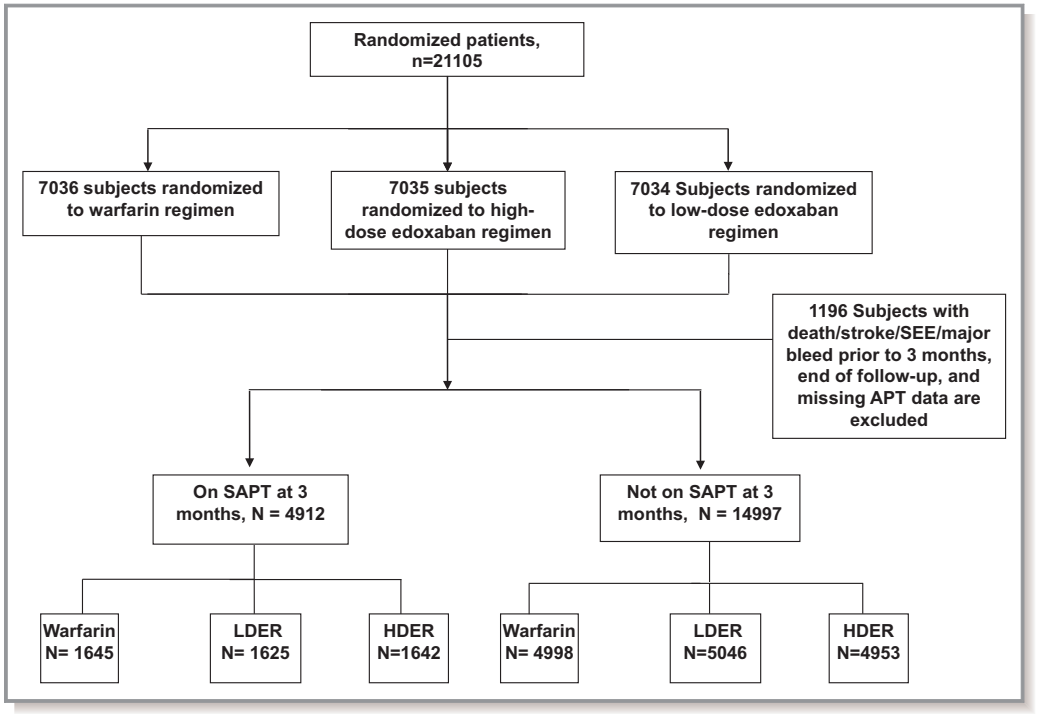

Figure 1. Study consort diagram. APT indicates antiplatelet therapy; HDER, high-dose edoxaban registry; LDER, low dose edoxaban regimen; SEE, systemic embolic event.

whom were taking ≤100 mg/day aspirin). The percentage of patients receiving aspirin at each time point were also similar (Table S1). The remainder received another antiplatelet agent, usually clopidogrel.

Patients receiving SAPT were more frequently male, smokers, and more likely to have a history of CAD, previous MI, previous coronary revascularization, dyslipidemia, diabetes, and carotid and peripheral arterial disease (Table 2), previous coronary revascularization, paroxysmal AF, a $CHADS_2$ score ≥4, a CHA_2DS_2-Vasc score ≥4, a HAS-BLED score ≥3, and to have been VKA naïve at the time of randomization. During the trial, the mTTR was lower in patients randomized to warfarin who were on SAPT (67.7%), compared to those who were not on SAPT (69.0%; *P*=0.002).

Outcomes in Patients With and Without SAPT

When the 3 arms (warfarin and the 2 edoxaban arms) were considered together, event rates for the primary efficacy endpoint (stroke/SEE) for those who received SAPT (1.71%/year) were similar to those in the non-SAPT group (1.56%/year; *P*=0.26). Adjusted HR (HR_{adj}; SAPT vs no SAPT) was 1.12 (95% CI, 0.95–1.32; *P*=0.19). Major bleeding occurred more frequently in patients who received SAPT (3.37%/year) than not (1.99%/year; *P*<0.001); HR_{adj}=1.46 (95% CI, 1.27–1.67; P<0.001; Figure 2).

In patients randomized to warfarin, those receiving SAPT had a numerically higher event rate for the primary endpoint

Table 1. Prevalence of SAPT Use at Randomization and 6 Time Points Throughout the Study

Landmark Period	Total, n/N (%)	Warfarin, n/N (%)	Low-Dose Edoxaban, n/N (%)	High-Dose Edoxaban, n/N (%)
At baseline	6678/21 105 (31.6)	2253/7036 (32.0)	2179/7034 (31.0)	2246/7035 (31.9)
At 3 months	4912/19 909 (24.7)	1645/6643 (24.8)	1625/6671 (24.4)	1642/6595 (24.9)
At 6 months	4618/19 276 (24.0)	1551/6425 (24.1)	1527/6481 (23.6)	1540/6370 (24.2)
At 12 months	4567/18 794 (24.3)	1541/6250 (24.7)	1524/6301 (24.2)	1502/6243 (24.1)
At 18 months	4574/18 470 (24.8)	1518/6147 (24.7)	1525/6201 (24.6)	1531/6122 (25.0)
At 24 months	4447/18 095 (24.6)	1460/6002 (24.3)	1492/6090 (24.5)	1495/6003 (24.9)
At 30 months	3279/13 225 (24.8)	1089/4392 (24.8)	1127/4439 (25.4)	1063/4394 (24.2)

SAPT indicates single antiplatelet therapy.

Table 2. Baseline Characteristics in Patients With and Without Antiplatelet Therapy at 3 Months (Including Low Edoxaban Group)

Variables	Not on SAPT (N=14 997)	On SAPT (N=4912)	*P* Value
Demographic			
Age, y, median (IQR)	72.0 (64.0–77.0)	72.0 (64.0–78.0)	0.515
Age ≥75 y, n (%)	5907 (39.4)	1973 (40.2)	0.333
Male, n (%)	9039 (60.3)	3346 (68.1)	0.000
Region (%)			
North America	2723 (18.2)	1662 (33.8)	0.000
Latin America	1996 (13.3)	496 (10.1)	
Western Europe	2485 (16.6)	508 (10.3)	
Eastern Europe	5634 (37.6)	1227 (25.0)	
Asia	2159 (14.4)	1019 (20.7)	
Clinical factors and medical history			
Weight ≤60 kg, n (%)	1408 (9.4)	483 (9.8)	0.356
CrCl at randomization			
Median (IQR), mL/min	71.1 (54.5–92.5)	70.0 (53.4–91.9)	0.013
≤50 mL/min, n (%)	2775 (18.5)	966 (19.7)	0.070
Current/former smoker, n (%)	5866 (39.1)	2287 (46.6)	0.000
Previous CAD, n (%)	4172 (27.8)	2403 (48.9)	0.000
Previous MI, n (%)	1395 (9.3)	869 (17.7)	0.000
Previous coronary revascularization, n (%)	1177 (7.8)	1274 (25.9)	0.000
Hypertension, n (%)	14 040 (93.6)	4606 (93.8)	0.705
Dyslipidemia, n (%)	7520 (50.1)	2979 (60.6)	0.000
Diabetes, n (%)	5190 (34.6)	1993 (40.6)	0.000
History of congestive heart failure, n (%)	8669 (57.8)	2762 (56.2)	0.053
Peripheral arterial disease, n (%)	511 (3.4)	278 (5.7)	0.000
Carotid arterial disease, n (%)	744 (5.0)	454 (9.2)	0.000
Previous stroke or TIA, n (%)	4216 (28.1)	1387 (28.2)	0.866
Type of AF			
Paroxysmal, n (%)	3530 (23.5)	1510 (30.8)	0.000
Persistent, n (%)	3376 (22.5)	1211 (24.7)	
Permanent, n (%)	8089 (53.9)	2189 (44.6)	
$CHADS_2$ score ≥4, n (%)	3243 (21.6)	1190 (24.2)	0.000
CHA_2DS_2-Vasc score ≥4, n (%)	10 301 (68.7)	3694 (75.2)	0.000
HAS-BLED score ≥3, n (%)	5253 (35.0)	3895 (79.3)	0.000
Medication			
VKA naïve, n (%)	5633 (37.6)	2459 (50.1)	0.000
Dose reduced at randomization, n (%)	3669 (24.5)	1265 (25.8)	0.070

AF indicates atrial fibrillation; CAD, coronary artery disease; CrCl, creatinine clearance; IQR, interquartile range; MI, myocardial infarction; TIA, transient ischemic attack; VKA, vitamin K antagonist.

(1.88%/year) compared to those in the non SAPT group (1.49%/year; *P*=0.08). In the HDER, the primary endpoint events were similar in the 2 groups (1.31%/year on SAPT vs 1.42%/year not on SAPT; *P*=0.61; Figure 3), and for the LDER they were 1.94 (on SAPT) and 1.78 (not on SAPT; *P*=0.49; Table 3).

In the warfarin arm, cardiovascular death occurred more frequently in patients receiving SAPT (3.56%/year) than not

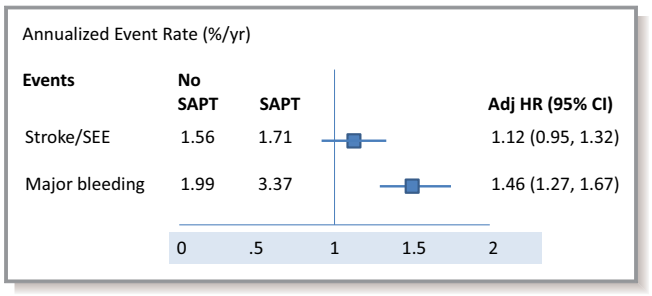

Figure 2. Outcomes in patients with and without antiplatelet therapy. Adj HR indicates adjusted hazard ratio; HR, hazard ratio; SAPT, single antiplatelet therapy; SEE, systemic embolic event.

receiving it (2.61%/year; P=0.001). In HDER, corresponding values were 2.94%/year versus 2.12%/year (P=0.002), respectively (Figure 3), whereas in LDER these values were 2.69% and 2.34% (P=0.19; Table 3).

In the warfarin arm the primary safety endpoint (ISTH major bleeding) occurred more frequently in patients receiving SAPT (4.38%/year) than not (2.54%/year; P<0.001). This was also the case for patients in the HDER (3.55% and 2.04%; P<0.001; Figure 4,) as well as in the LDER (2.23% and 1.41%, respectively; P=0.001; Table 4).

Efficacy of Edoxaban Versus Warfarin Stratified by SAPT

HRs_{adj} values for the primary endpoint (stroke/SEE) for HDER versus warfarin were 0.70 (95% CI, 0.50–0.98) in the SAPT group and 0.94 (95% CI, 0.77–1.15) in the non-SAPT group (P_{int}=0.14; Figure 3). Corresponding HRs_{adj} values for the LDER versus warfarin comparisons were 1.03 (95% CI, 0.76–1.39) on SAPT and 1.19 (95% CI, 0.99–1.43) for not on SAPT, respectively (P_{int}= 0.42). Similar findings were noted for ischemic stroke (Table 3).

HRs_{adj} values for HDER versus warfarin for cardiovascular death were similar for those in the SAPT group (HR=0.83; 95% CI, 0.66–1.05) and in the non-SAPT group (HR_{adj}=0.81; 95% CI, 0.69–0.94; P_{int}=0.83; Figure 3). The corresponding comparisons of HRs_{adj} in LDER versus warfarin were 0.75 (95% CI, 0.59–0.95) and 0.89 (95% CI, 0.77–1.04; P_{int}=0.21.) (Table 3).

HRs_{adj} values for safety of edoxaban versus warfarin stratified by SAPT for the primary safety endpoint (ISTH major bleeding) were 0.82 (95% CI, 0.65–1.03) in the SAPT group and 0.80 (95% CI, 0.68–0.95) in the non-SAPT group (P_{int}=0.91), whereas corresponding HRs_{adj} value for the LDER versus warfarin were 0.51 (95% CI, 0.39–0.66) and 0.56 (95% CI, 0.46–0.67; P_{int}=0.59). There were consistent reductions in bleeding (including ICH, life-threatening bleeding, and fatal

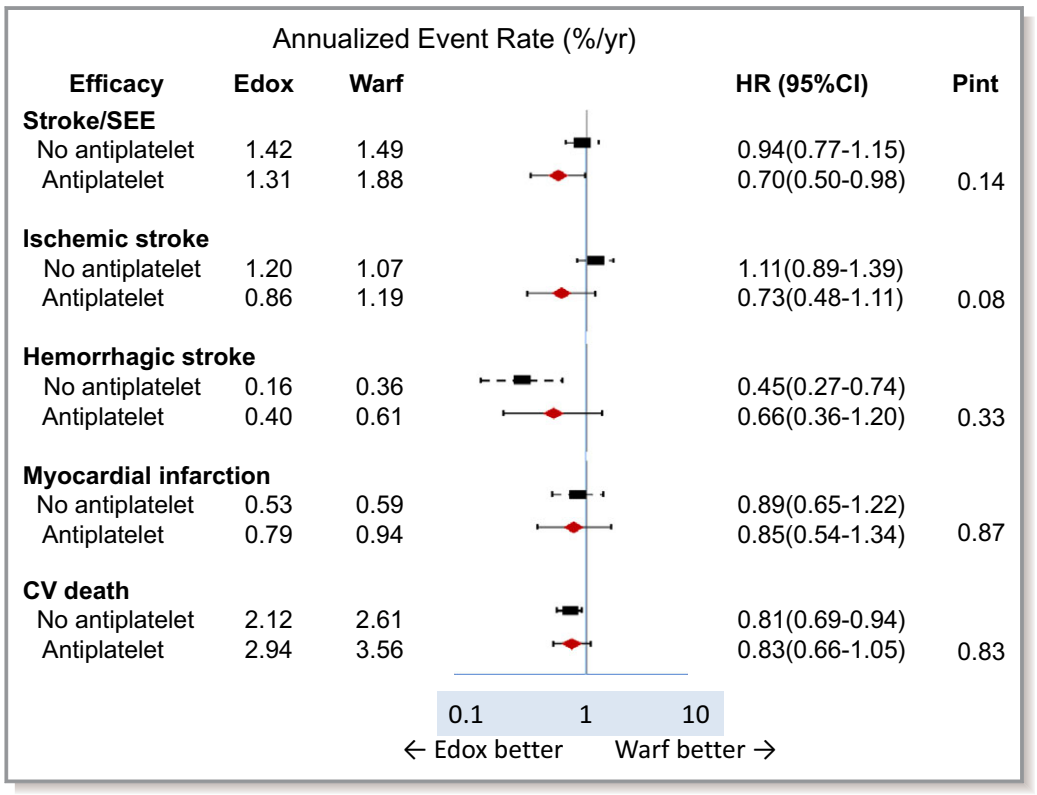

Figure 3. Efficacy endpoints of high dose edoxaban strategy vs warfarin in patients with and without antiplatelet therapy. CV death indicates cardiovascular death; Edox, edoxaban; HR, hazard ratio; SEE, systemic embolic event; Warf, warfarin.

Table 3. Efficacy Endpoints of Low Dose Edoxaban Strategy

Outcome	Annualized Event Rate (%/year)		LDE vs WAR	
	LDE	WAR	HR (95% CI)	P_{int}
Stroke/SEE				
No antiplatelet	1.78	1.49	1.19 (0.99–1.43)	
Antiplatelet	1.94	1.88	1.03 (0.76–1.39)	0.42
Ischemic stroke				
No antiplatelet	1.55	1.07	1.44 (1.17–1.78)	
Antiplatelet	1.64	1.19	1.37 (0.96–1.96)	0.83
Hemorrhagic stroke				
No antiplatelet	0.14	0.36	0.38 (0.22–0.65)	
Antiplatelet	0.18	0.61	0.29 (0.13–0.64)	0.59
Myocardial infarction				
No antiplatelet	0.76	0.59	1.29 (0.97–1.72)	
Antiplatelet	0.89	0.94	0.95 (0.61–1.47)	0.24
Cardiovascular death				
No antiplatelet	2.34	2.61	0.89 (0.77–1.04)	
Antiplatelet	2.69	3.56	0.75 (0.59–0.95)	0.21

HR indicates adjusted hazard ratio; LDE, low dose edoxaban strategy; SEE, systemic embolic event; WAR, warfarin.

bleeding) with both edoxaban regimens compared to warfarin, with and without concomitant SAPT (Figure 4; Table 4).

The prespecified net clinical outcome, which consisted of both efficacy and safety endpoints, occurred significantly more frequently in patients in the SAPT group, in all 3 arms (warfarin and both edoxaban arms; Figure 4; Table 4). HRs_{adj} value of HDER to warfarin were similar in the 2 groups as well, with HRs_{adj} of 0.82 (95% CI, 0.71–0.95) and 0.89 (95% CI, 0.81–0.98) in the SAPT and non-SAPT groups, respectively (P_{int}=0.35; Figure 4). Corresponding values for HRs_{adj} of LDER to warfarin were 0.72 (95% CI: 0.62–0.84) and 0.89 (95% CI, 0.81–0.98; P_{int}=0.02; Table 4).

Sensitivity Analyses Stratified by SAPT at Randomization

The results of the sensitivity analysis for the comparison of outcomes of the edoxaban regimen compared to warfarin stratified by SAPT at randomization yielded similar results to those in the principal analysis, described above.

Findings With Aspirin

The results presented in Figures 3 and 4 and in Tables S2 and S3 for all patients receiving SAPT, were quite similar for the

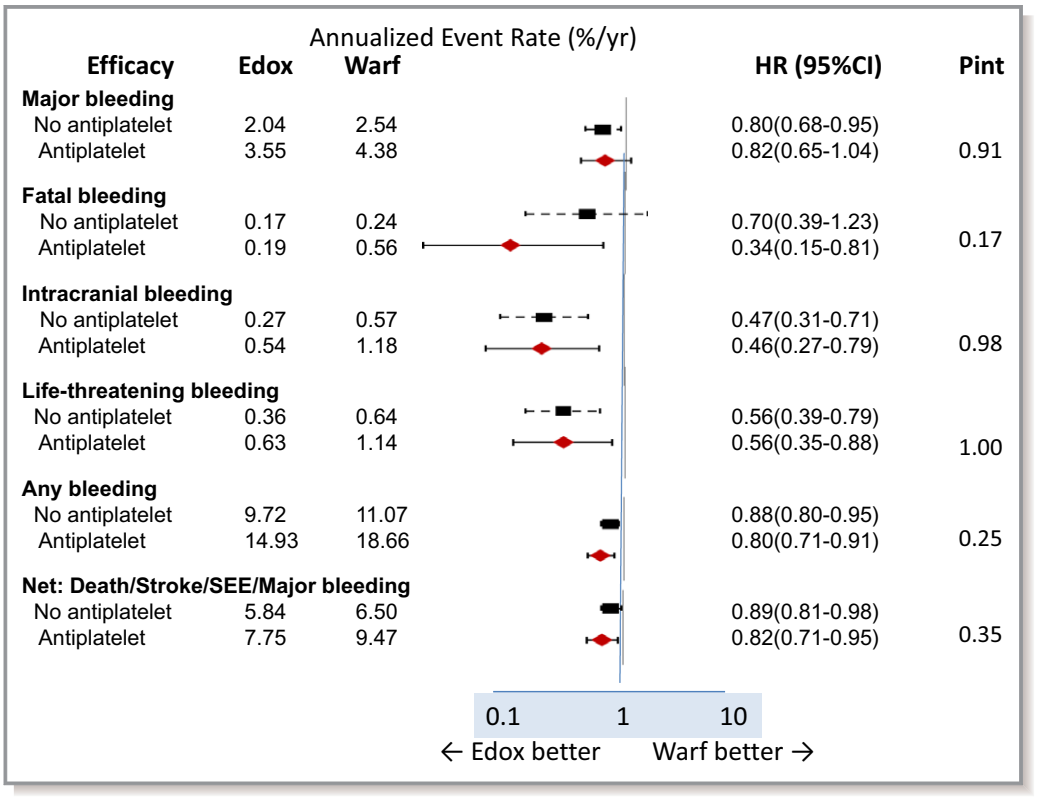

Figure 4. Bleeding endpoints and net clinical outcome of high dose edoxaban strategy vs warfarin in patients with and without antiplatelet therapy. Edox indicates edoxaban; HR, hazard ratio; SEE, systemic embolic event; Warf, warfarin.

Table 4. Bleeding Endpoint and Net Clinical Outcome of LDE

	Annualized Event Rate (%/year)		LDE vs WAR	
Safety	LDE	WAR	HR (95% CI)	P_{int}
Major bleeding				
No antiplatelet	1.41	2.54	0.56 (0.46–0.67)	
Antiplatelet	2.23	4.38	0.51 (0.39–0.66)	0.59
Fatal bleeding				
No antiplatelet	0.11	0.24	0.47 (0.25–0.9)	
Antiplatelet	0.13	0.56	0.23 (0.09–0.61)	0.22
Intracranial bleeding				
No antiplatelet	0.23	0.57	0.40 (0.26–0.62)	
Antiplatelet	0.21	1.18	0.18 (0.08–0.37)	0.07
Life-threatening				
No antiplatelet	0.34	0.64	0.52 (0.37–0.74)	
Antiplatelet	0.31	1.14	0.28 (0.15–0.5)	0.07
Any bleeding				
No antiplatelet	7.47	11.07	0.67 (0.62–0.74)	
Antiplatelet	13.04	18.66	0.69 (0.61–0.79)	0.73
Net: death/stroke/SEE/major bleeding				
No antiplatelet	5.81	6.50	0.89 (0.81–0.98)	
Antiplatelet	6.91	9.47	0.72 (0.62–0.84)	0.02

HR indicates adjusted hazard ratio; LDE, low dose edoxaban strategy; SEE, systemic embolic event; WAR, warfarin.

large subgroup (92.5%) of SAPT patients receiving aspirin (Tables S2 and S3).

Discussion

Current guidelines recommend that low-dose aspirin (75–100 mg/day) and/or a P_2Y12 antagonist may be given concurrently with an anticoagulant to prevent myocardial ischemic events and stroke in AF patients after coronary revascularization, a recent acute coronary syndrome or with high-risk CAD. The associated increased risk of bleeding should be evaluated and efforts made to minimize it whenever possible.[10,14–18] Also, the American Heart Association/American College of Cardiology Foundation guideline for secondary prevention in patients with AF and coronary or other atherosclerotic vascular disease recommends treatment with warfarin and low-dose aspirin (≤100 mg daily).[14] However, for AF patients with stable coronary or peripheral arterial disease (ie, no acute events or revascularization for ≥12 months), oral anticoagulant therapy without antiplatelet therapy may be considered.[10,16] In clinical practice, a combination of anticoagulant and dual antiplatelet therapy (triple antithrombotic therapy) may be administered, preferably for short periods in patients with AF who are at very high risk of a platelet-driven event, such as patients with a recent acute coronary syndrome or stent implantation.[19] This increases the risk of serious bleeding and it should be reduced to double therapy (ie, an anticoagulant together with SAPT) whenever, or as soon as, possible.

The present report from the ENGAGE AF-TIMI 48 trial provides data on the relative efficacy and safety of combination antithrombotic therapy. At the time of enrollment, approximately one-third of patients were receiving SAPT, usually aspirin. SAPT was discontinued in one quarter of these patients after randomization to anticoagulant therapy. SAPT was prescribed by the treating physician more commonly in patients with established CAD, diabetes, dyslipidemia, peripheral arterial disease, and those who were therefore at higher risk of development of acute coronary syndromes than were patients without these comorbidities. SAPT administration was used most frequently in North America and less frequently elsewhere. This difference may be explained, at least in part, by the greater frequency of patients at high risk enrolled in North America.

We observed that the addition of SAPT to an anticoagulant (warfarin or edoxaban) was associated with a significantly greater risk of bleeding. However, the addition of SAPT did not modify the relative efficacy and safety of edoxaban as compared to warfarin. Notably, when compared to warfarin, both edoxaban regimens significantly reduced all forms of bleeding, including ICH and life-threatening bleeding, both in patients who were as well as those who were not, receiving a SAPT.

The trade-off between benefit and safety of adding SAPT to an anticoagulant in patients with both AF and CAD or others at risk of an acute coronary event is often challenging for clinicians.[9,10] A meta-analysis of 10 randomized trials comparing the combination of an oral anticoagulant and aspirin with anticoagulant alone in patients with AF at risk of coronary events showed no reduction in arterial thromboembolic events in favor of the combination, but did show an increased risk of major bleeding.[20] Lamberts et al. examined the efficacy and safety of adding aspirin to a VKA in AF patients with stable CAD in a nation-wide Danish registry.[8] Like the meta-analysis, they found that the risk of coronary events with the combination was similar to that observed with VKA alone, whereas the risk of bleeding increased significantly when aspirin or clopidogrel were added to VKA. The WOEST (What is the Optimal antiplateElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing) trial compared dual therapy (VKA plus clopidogrel) to triple therapy (VKA, clopidogrel and aspirin) in patients receiving oral anticoagulants undergoing PCI. Dual therapy was associated with a significant reduction in bleeding without an increase in rate of thrombotic events.[21]

Our results with edoxaban are generally consistent with earlier studies. The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE,) [22] and the Rivaroxaban Once-daily, oral, direct Factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF)[23] trials showed that concomitant aspirin use did not alter the relative effects of apixaban and rivaroxaban on stroke/SEE and major bleeding compared to warfarin. In the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial, the addition of SAPT did not affect the safety and relative efficacy of dabigatran 110 mg BID when compared to warfarin. However, in contrast to our findings, the effect of dabigatran 150 mg BID on the reduction of stroke/SEE appeared to be attenuated among patients receiving an antiplatelet agent (HR, 0.80) in comparison to those who were not (HR=0.52, P_{int}=0.058).[24]

Limitations

Patients with recent acute coronary syndrome, or recent stent implantation were excluded from this trial. Therefore, the results may be applicable only to patients in whom a single antiplatelet agent may be indicated. One of the limitations of this analysis is that it was based on SAPT at 3 months rather than at randomization, because a sizeable percentage of patients (25%) discontinued SAPT after they entered the ENGAGE AF trial. Therefore, the events occurring during the first 3 months post-randomization were not included in the analysis reported herein. However, the sensitivity analysis which included all patients who entered the trial exhibited similar results. Administration of SAPT was not randomized, and although the analyses were adjusted for the baseline characteristics, such adjustments are never complete. In the future, randomized controlled trials on the outcomes of new oral anticoagulants with and without SAPT would be informative.

Conclusions

Patients with nonvalvular AF who were prescribed a single antiplatelet agent along with concomitant anticoagulant therapy had higher risks of bleeding than those who were prescribed only an anticoagulant. However, combination therapy did not alter the reduction in bleeding in both dose strategies of edoxaban compared with well-managed warfarin. All forms of bleeding were highest in patients randomized to warfarin who were treated with a SAPT. Because of this finding, patients with AF who are deemed to require the addition of a SAPT should receive a Xa inhibitor for anticoagulation whenever possible.

Sources of Funding

The ENGAGE AF TIMI 48 trial was funded by Daiichi Sankyo Pharma Development, Edison, NJ).

Disclosures

Dr Xu, Dr Nordio and Ms Murphy have no disclosures. Drs Patel, Shi, and Mercuri are employees of Daiichi Sankyo, which funded this trial. Dr Ruff reports grant support through his institution from Daiichi-Sankyo and has served as a consultant and received honoraria from Daiichi-Sankyo, Boehringer Ingelheim, Bayer, and Portola; and grant support through his institution outside the submitted work from AstraZeneca, Eisai, Intarcia and GlaxoSmithKline (GSK). Dr Giugliano has served as a consultant and had received honoraria from Bristol-Myers Squibb, Janssen, Daiichi-Sankyo, Merck, and Sanofi; and grant support through his institution from Daiichi-Sankyo, Merck, Johnson & Johnson, Sanofi, and AstraZeneca. Dr Antman reports receiving grant support through his institution from Daiichi-Sankyo. Dr Braunwald reports grants (through the Brigham and Women's Hospital) and personal fees for lectures from Daiichi-Sankyo. He has received grants from Duke University, AstraZeneca, Merck & Co, and GSK; uncompensated fees for consultancy from Merck & Co, personal fees for consultancies from Genyzme, Medicines Co, and Sanofi-Aventis; uncompensated personal fees for lectures from Merck, and personal fees for lectures from Menarini International and Medscape.

References

1. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369:2093–2104.
2. Kralev S, Schneider K, Lang S, Süselbeck T, Borggrefe M. Incidence and severity of coronary artery disease in patients with atrial fibrillation undergoing first-time coronary angiography. *PLoS One*. 2011;6:e24964.
3. Rodríguez-Mañero M, Bertomeu-González V, Cordero A, Moreno-Arribas J, Mazón P, Fácila L, Cosín J, Galve E, Lekuona I, González-Juanatey JR, Bertomeu-Martínez V. Trends in clinical profile and medical treatments of atrial fibrillation patients over the last 10 years. *Rev Port Cardiol*. 2013;32:103–109.
4. ACTIVE Writing Group of the ACTIVE Investigators, Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, Pfeffer M, Hohnloser S, Yusuf S. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet*. 2006;367:1903–1912.
5. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002;324:71–86.
6. Hansen ML, Sørensen R, Clausen MT, Fog-Petersen ML, Raunsø J, Gadsbøll N, Gislason GH, Folke F, Andersen SS, Schramm TK, Abildstrøm SZ, Poulsen HE, Køber L, Torp-Pedersen C. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Arch Intern Med*. 2010;170:1433–1441.
7. Lamberts M, Gislason GH, Olesen JB, Kristensen SL, Schjerning Olsen AM, Mikkelsen A, Christensen CB, Lip GY, Køber L, Torp-Pedersen C, Hansen ML. Oral anticoagulation and antiplatelets in atrial fibrillation patients after

myocardial infarction and coronary intervention. *J Am Coll Cardiol*. 2013;62:981–989.

8. Lamberts M, Gislason GH, Lip GYH, Lassen JF, Oleson JB, Mikkelsen AP, Sørensen R, Kober L, Torp-Pedersen C, Hansen ML. Antiplatelet therapy for stable coronary artery disease in atrial fibrillation patients on oral anticoagulant: a nationwide cohort study. *Circulation*. 2014;129:1577–1585.
9. Lane DA, Raichand S, Moore D, Connock M, Fry-Smith A, Fitzmaurice DA. Combined anticoagulation and antiplatelet therapy for high-risk patients with atrial fibrillation: a systematic review. *Health Technol Assess*. 2013;17:1–188.
10. Lip GY, Windecker S, Huber K, Kirchhof P, Marin F, ten Berg JM, Haeusler KG, Boriani G, Capodanno D, Gilard M, Zeymer U, Lane D. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: a joint consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS). *Eur Heart J*. 2014;35:3155–3179.
11. Ruff CT, Giugliano RP, Antman EM, Crugnale SE, Bocanegra T, Mercuri M, Hanyok J, Patel I, Shi M, Salazar D, McCabe CH, Braunwald E. 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;160:635–641.
12. Weitz JI. Hemostasis, thrombosis, fibrinolysis and cardiovascular disease. In: Mann DL, Zipes DP, Libby P, Bonow RO, eds. *Braunwald's Heart Disease*. 10th ed. Philadelphia, PA: Elsevier; 2015:1809–1833.
13. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trial. *Lancet*. 2014;383:955–962.
14. January CT, Wann LS, Alpert JS, Calkins H,Cigarroa JE,Cleveland Jr JC,Conti JB, Ellinor PT,Ezekowitz MD,Field ME,Murray KT,Sacco RL,Stevenson WG,Tchou PJ, Tracy CM,Yancy CW; ACC/AHA Task Force Members. 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;130:e199–e267.
15. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. *Chest*. 2010;137:263–272.
16. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P. 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;33:2719–2747.
17. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG, Yancy CW. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127:e362–e425.
18. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2014;35:2541–2619.
19. Potpara TS, Lip GY, Dagres N, Estner HL, Larsen TB, Blomström-Lundqvist C. Management of acute coronary syndrome in patients with non-valvular atrial fibrillation: results of the European Heart Rhythm Association Survey. *Europace*. 2014;16:293–298.
20. Dentali F, Douketis JD, Lim W, Crowther M. Combined aspirin-oral anticoagulant therapy compared with oral anticoagulant therapy alone among patients at risk for cardiovascular disease: a meta-analysis of randomized trials. *Arch Intern Med*. 2007;167:117–124.
21. Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, Adriaenssens T, Vrolix M, Heestermans AA, Vis MM, Tijsen JG, van t Hof AW, ten Berg JM; WOEST study investigators. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet*. 2013;381:1107–1115.
22. Alexander JH, Lopes RD, Thomas L, Alings M, Atar D, Aylward P, Goto S, Hanna M, Huber K, Husted S, Lewis BS, McMurray JJ, Pais P, Pouleur H, Steg PG, Verheugt FW, Wojdyla DM, Granger CB, Wallentin L. Apixaban vs. warfarin with concomitant aspirin in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Eur Heart J*. 2014;35:224–232.
23. Mahaffey KW, Stevens SR, White HD, Nessel CC, Goodman SG, Piccini JP, Patel MR, Becker RC, Halperin JL, Hacke W, Singer DE, Hankey GJ, Califf RM, Fox KA, Breithardt G. Ischaemic cardiac outcomes in patients with atrial fibrillation treated with vitamin K antagonism or factor Xa inhibition: results from the ROCKET AF trial. *Eur Heart J*. 2014;35:233–241.
24. Dans AL, Connolly SJ, Wallentin L, Yang S, Nakamya J, Brueckmann M, Ezekowitz M, Oldgren J, Eikelboom JW, Reilly PA, Yusuf S. Concomitant use of antiplatelet therapy with dabigatran or warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. *Circulation*. 2013;127:634–640.