Table 1. Clinical Outcomes in the IMPACT Study[a]

Outcome	Control Group (n=1361)		Intervention Group (n=1357)		Hazard Ratio	p Value
	n	Rate	n	Rate		
Primary endpoint	61	2.3	63	2.4	1.06	0.732
Mortality	140	5.1	147	5.4	1.07	0.662
Thromboembolism	37	1.4	32	1.2	0.88	0.586
Ischemic stroke	28	1.0	22	0.8	0.79	0.417
Systemic embolism	2		0		—	0.969
TIA	8		10		1.27	0.619
Hemorrhagic stroke	3	0.1	3	0.1	1.03	0.973
Other major bleed	32	1.2	43	1.6	1.39	0.145

IMPACT=Combined Use of BIOTRONIK Home Monitoring and Predefined Anticoagulation to Reduce Stroke Risk Trial; TIA=transient ischemic attack.

[a]Rates are expressed as the number of events per 100 patient-years.

The primary end point was the occurrence of the first stroke, systemic embolism, or major bleeding event. The secondary end points were all-cause mortality, all stroke, and AT burden.

The study was prematurely terminated on June 13, 2013, after the Data Monitoring Committee determined futility once 75% of expected events accrued. Cumulative follow-up included 5430 patient-years and median exposure of 701 days.

There were no differences in baseline characteristics except that 34.5% of the intervention group were taking antiplatelet therapy other than aspirin, compared with 30.7% of the control group (p=0.037). ATs were detected in 493 patients (36.3%) in the intervention group and 452 patients (33.2%) in the control group (p=0.0908). Of these, 126 patients in the intervention group and 115 in the control group had confirmed atrial fibrillation (AF) meeting the OAC criteria. The median $CHADS_2$ score was 2 (p=0.544), and 64% of patients in each group had ICDs.

Among patients with AF meeting OAC criteria, 91 (72.2%) in the intervention group and 69 (60.0%) in the control group started OAC therapy. Forty-six patients (36.5%) in the intervention group and 29 (25.2%) in the control group stopped OACs. Mean days on OACs were 409 in the intervention group and 450 in the control group. Adherence to the OAC protocol was observed in 126 patients, 45.2% started OAC within the specified time frame, and the time within the therapeutic range was 61.2% in patients taking vitamin K antagonists.

There were no significant differences between the groups for any endpoint. The rate of the primary end point was 2.4% in the intervention group and 2.3% in the control group (HR, 1.06; p=0.732; Table 1). There was no temporal relationship between the occurrence of device-detected AT and TE events, suggesting that an accelerated OAC strategy did not improve the prevention of TE, said Dr. Halperin

Limitations of this study include suboptimal adherence with the OAC protocol and greater use of antiplatelet therapy in the intervention group. The low event rate limited the power to detect between-group differences in outcomes.

Starting and stopping OAC on the basis of device-detected AF did not improve clinical outcomes in the IMPACT study. Dr. Halperin concluded that the decision to start OAC therapy for device-detected AF should be based on a comprehensive clinical assessment of risk and benefit and that the absence of device-detected AF should not lead to the discontinuation of OAC.

Edoxaban Noninferior to Warfarin for Stroke Prevention in AF

Written by Wayne Kuznar

Robert P. Giugliano, MD, SM, Brigham and Women's Hospital, Boston, Massachusetts, USA, presented the results of the Global Study to Assess the Safety and Effectiveness of Edoxaban (DU-176b) Versus Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation [ENGAGE-AF TIMI 48; Giugliano RP et al. *N Engl J Med* 2013] and new secondary analyses.

In ENGAGE-AF TIMI 48, the new oral anticoagulant (NOAC) edoxaban was studied in 21,105 patients who had atrial fibrillation (AF) and $CHADS_2$ scores ≥2. Patients were randomly assigned in a 1:1:1 double-blind, double-dummy fashion to warfarin (target international normalized ratio [INR] 2.0 to 3.0), high-dose edoxaban (60 mg/day), or low-dose edoxaban (30 mg/day). The objective of the study was to establish the noninferiority of once-daily edoxaban compared with warfarin.

The dose of edoxaban was reduced by half in about 25% of patients at randomization for creatinine clearance between 30 and 50 mL/min, if the patient weighed ≤60 kg, or in the presence of a strong P-glycoprotein inhibitor, and it was adjusted (increased or decreased) in 8.3% after randomization. After a median follow-up

period of 2.8 years, patients in the warfarin arm spent a median of 68.4% of the time in therapeutic range.

The primary end point of stroke or systemic embolic event (SEE) was lower with high-dose edoxaban compared with warfarin (HR, 0.79; p<0.0001 for noninferiority) but not for low-dose edoxaban (HR, 1.07; p=0.005 for noninferiority) in the modified intention-to-treat analysis. In a superiority analysis in the intention-to-treat protocol, compared with warfarin, there was a favorable trend toward a reduction in the primary end point with high-dose edoxaban (HR, 0.87; p=0.08), and with low-dose edoxaban there was an unfavorable trend (HR, 1.13; p=0.10).

The composite secondary endpoint of stroke, SEE, or cardiovascular death was lower with high-dose edoxaban (HR, 0.87; p=0.005) compared with warfarin, while it was similar between low-dose edoxaban (HR, 0.95; p=0.32) and warfarin.

The secondary end point of risk for hemorrhagic stroke was reduced by 46% with high-dose edoxaban and by 67% with low-dose edoxaban compared with warfarin (p<0.001 for both comparisons). For the secondary endpoint of ischemic stroke, compared with warfarin, the HR was 1.00 (p=0.97) with high-dose edoxaban and 1.41 with low-dose edoxaban (p<0.001), indicating that low-dose edoxaban did not protect from ischemic stroke as well as well-managed warfarin.

The primary safety endpoint of major bleeding, evaluated by the modified International Society on Thrombosis and Haemostasis criteria, compared with warfarin, occurred significantly less often with high-dose edoxaban (HR, 0.80; p<0.001) and was markedly reduced with low-dose edoxaban (HR, 0.47; p<0.001).

Dr. Giugliano also presented several secondary findings, including a meta-analysis of recent trials, and 3 additional analyses from ENGAGE-AF TIMI 48 in patients by AF pattern, an in-depth analysis of cerebrovascular events, and explorations of the relationship between edoxaban dose, drug concentrations, anticoagulant activity, and outcomes.

META-ANALYSIS OF 4 NOAC TRIALS

A meta-analysis of the 4 major trials of the NOACs showed a 19% overall reduction in the rate of stroke or SEE with these agents compared with warfarin ((p≤0.0001) and a 10% reduction in all-cause mortality (p=0.0003) [Ruff CT et al. *Lancet* 2014].

Transition to Open-Label Anticoagulation

In ENGAGE-AF TIMI 48, a detailed transition plan at the end of the trial permitted transition to any approved oral anticoagulant, and use of a transition kit, frequent INR monitoring, and an algorithm for those transitioning to vitamin K antagonists (VKAs). During a 30-day transition period to open-label warfarin, there were 7 strokes (1 hemorrhagic) in each treatment group, and the rates of major bleeding events through day 14 were similar (Table 1). Of the patients randomly assigned to edoxaban, 85% and 99% had therapeutic INR values by Days 14 and 30, respectively. The transition from edoxaban to open-label anticoagulation at the end of the ENGAGE-AF TIMI 48 study was safe if open-label VKA was closely monitored, Dr. Giugliano said.

Table 1. Outcomes in ENGAGE-AF TIMI 48 During Transition From Edoxaban to Warfarin

Events After Transition to Open-Label Anticoagulant	Warfarin (n=4503)	High-Dose Edoxaban (n=4526)	Low-Dose Edoxaban (n=4613)
Stroke or SEE through 30 d	7 (0.16%)	7 (0.15%)	7 (0.15%)
Major bleeds through 14 d	6 (0.13%)	4 (0.09%)	5 (0.11%)

ENGAGE-AF TIMI 48=Global Study to Assess the Safety and Effectiveness of Edoxaban (DU-176b) Versus Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation; SEE=systemic embolic event.

Outcomes by AF Pattern

In ENGAGE-AF TIMI 48, patients with paroxysmal AF had lower rates of stroke and death compared with those with persistent or permanent AF after multivariate adjustment. Major bleeding rates were similar across AF subtypes. Analyses comparing the multiple efficacy and safety outcomes of edoxaban with those of warfarin showed no significant interactions between the treatment group and the subtype of AF (paroxysmal, persistent, or permanent). Thus, the efficacy and safety profile of edoxaban was consistent regardless of the subtype of AF.

Correlations of Dose, Concentration, Factor Xa Activity, and Outcomes

The 4-fold dose range of edoxaban studied translated into a 3-fold range of edoxaban concentration and level of factor Xa activity. Dose reduction resulted in improved safety and similar efficacy as was observed for those who did not require dose reduction. However, patients who were reduced from 30 to 15 mg had a significantly greater risk for stroke or SEE compared with those taking warfarin (p=0.02).