Efficacy and Safety of Edoxaban in Patients With Active Malignancy and Atrial Fibrillation: Analysis of the ENGAGE AF-TIMI 48 Trial

Christina L. Fanola, MD, MSc; Christian T. Ruff, MD, MPH; Sabina A. Murphy, MPH; James Jin, PhD; Anil Duggal, MD; Noe A. Babilonia, MD; Piyamitr Sritara, MD; Michele F. Mercuri, MD, PhD; Pieter W. Kamphuisen, MD; Elliott M. Antman, MD, Eugene Braunwald, MD; Robert P. Giugliano, MD, SM

Background-

Anticoagulation in patients with malignancy and atrial fibrillation is challenging because of enhanced risks for thrombosis and bleeding and the frequent need for invasive procedures. Data on direct oral antagonists in such patients are sparse.

Methods and Results-

The ENGAGE AF-TIMI 48 (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction Study 48) trial randomized 21 105 patients with atrial fibrillation to edoxaban or warfarin.

Patients with malignancy, defined as a postrandomization new diagnosis or recurrence of remote cancer, were followed up over a median of 2.8 years. Adjusted Cox proportional hazard models were used to evaluate the safety and efficacy of edoxaban versus warfarin. Over a median of 495 days (interquartile range, 230–771 days), 1153 patients (5.5%) were diagnosed with new or recurrent malignancy, most commonly involving the gastrointestinal tract (20.6%), prostate (13.6%), and lung (11.1%). Malignancy was associated with increased risk of death (adjusted hazard ratio [HR], 3.12; 95% confidence interval [CI], 2.78–3.50) and major bleeding (adjusted HR, 2.45; 95% CI, 2.07–2.89), but not stroke/systemic embolism (adjusted HR, 1.08; 95% CI, 0.83–1.42). Relative outcomes with higher-dose edoxaban versus warfarin were consistent regardless of malignancy status for stroke/systemic embolism (HR, 0.60 [95% CI, 0.31–1.15] for malignancy versus HR, 0.89 [95% CI, 0.76–1.05] for no malignancy; interaction P=0.25) and major bleeding (HR, 0.98 [95% CI, 0.69–1.40] for malignancy versus HR, 0.79 [95% CI, 0.69–1.05] for no malignancy; interaction P=0.31). There was, however, a significant treatment interaction for the composite ischemic end point (ischemic stroke/systemic embolism/myocardial infarction), with greater efficacy of higher-dose edoxaban versus warfarin in patients with malignancy (HR, 0.54; 95% CI, 0.31–0.93) compared with no malignancy (HR, 1.02; 95% CI, 0.88–1.18; interaction P=0.026).

Conclusions-

In patients with atrial fibrillation who develop malignancy, the efficacy and safety profile of edoxaban relative to warfarin is preserved, and it may represent a more practical alternative.

(J Am Heart Assoc. 2018;7:e008987. DOI: 10.1161/JAHA.118.008987)

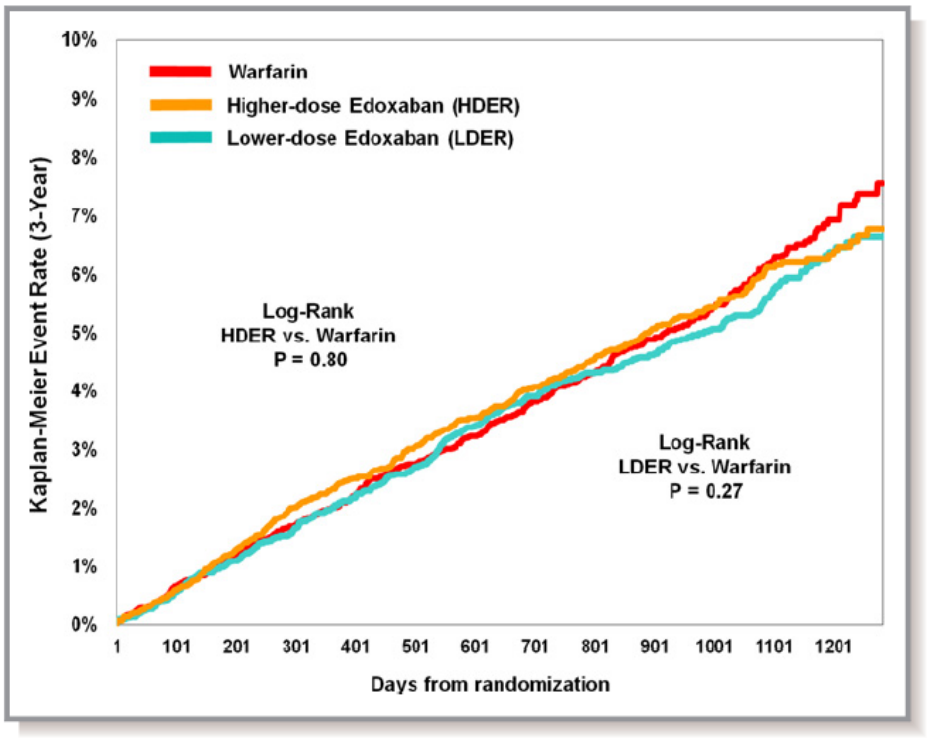

Figure 1. Kaplan-Meier curve of time to diagnosis of malignancy by treatment arm. HDER indicates higher-dose edoxaban regimen; LDER, lower-dose edoxaban regimen.

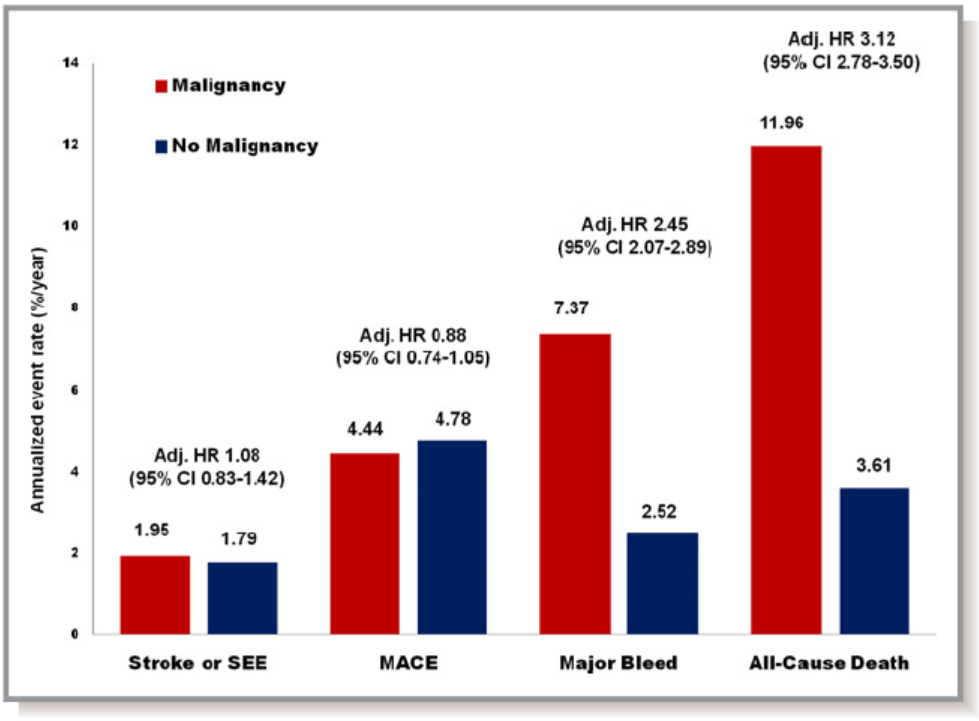

Figure 2. Adjusted (Adj.) risk of major end points in patients with vs without an active malignancy. Risk presented as Adj. hazard ratio (HR) with 95% confidence interval (CI). Malignancy status defined as those with new or recurrent advanced malignancy during a median 2.8-year follow-up period. MACE indicates major adverse cardiovascular event (myocardial infarction, stroke, or death attributable to cardiovascular cause or bleeding); SEE, systemic embolic event.