Beneficial Effects of Once-Daily Edoxaban in Patients With AF

Written by Brian Hoyle

Robert P. Giugliano, MD, SM, Harvard Medical School, Boston, Massachusetts, USA, and senior investigator of the Thrombosis In Myocardial Infarction (TIMI) study group, reported the results of the Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–TIMI 48 trial [ENGAGE AF-TIMI 48]. This randomized, double-blind, double-dummy trial of 21,105 patients demonstrated the efficacy and safety of a once-daily regimen of the oral anticoagulant edoxaban in treatment of atrial fibrillation (AF). The primary trial results have been published [Giugliano RP et al. *N Engl J Med* 2013].

Patients with ≥1 confirmed episode of AF within the past 12 months prior to enrollment were randomly assigned to receive warfarin, high-dose edoxaban 60 mg once daily, or low-dose edoxaban 30 mg once daily (Figure 1).

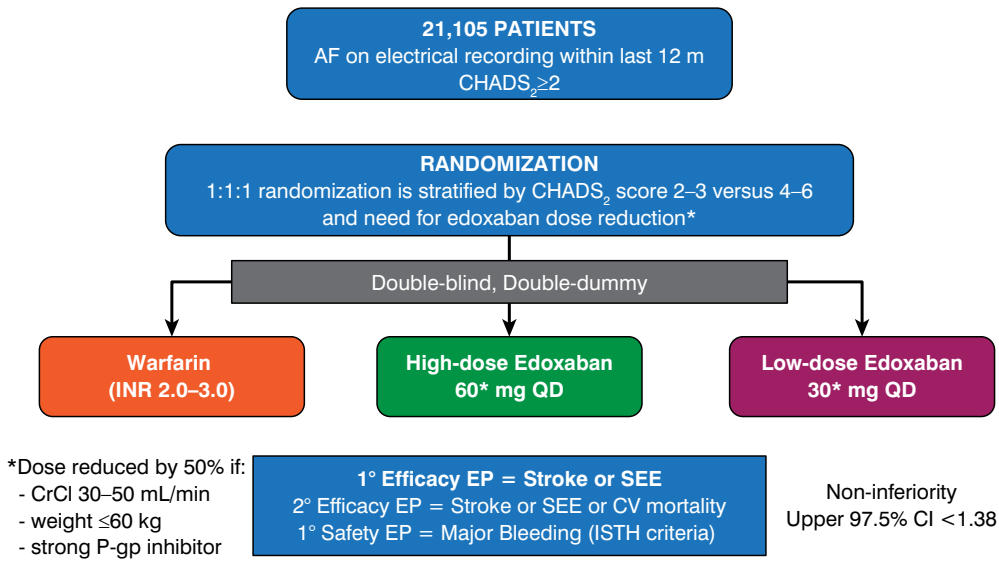
The edoxaban doses were reduced from 60 to 30 mg and from 30 to 15 mg at the time of randomization for patients with creatinine clearance of 30 to 50 mL/min, those weighing ≤60 kg, and those who were using cardiac medications that potently inhibited P-glycoprotein, or during the study if these conditions developed. The patient completion rate was 99.5%, with only 1 patient lost during the median 2.8-year follow-up period. Analyses included primary efficacy (noninferiority) for all patients receiving ≥1 dose (modified intention-to-treat [ITT]) while on treatment, superiority analyses in the ITT population counting all events after randomization, and principal safety (major bleeding) in the on-treatment population.

The primary end point was occurrence of stroke or systematic embolic events during follow-up. In the noninferiority modified ITT analysis, both low and high doses of edoxaban were noninferior to warfarin ($p < .001$ and $p = .005$, respectively). In the ITT analysis, neither dose of edoxaban was shown to be significantly different from warfarin ($p = .08$, $p = .10$, respectively) (Figure 2).

Analyses of secondary outcomes of edoxaban versus warfarin revealed superiority of edoxaban in terms of hemorrhagic stroke (both doses); secondary events including stroke, systematic embolic events, and cardiovascular death (60 mg); death or intracranial hemorrhage (both doses); all-cause mortality (30 mg); and cardiovascular death (both doses) (Figure 3).

Both the 30- and 60-mg edoxaban doses were superior to warfarin concerning major bleeding ($p < .001$ for both), fatal bleeding ($p < .001$ and $p = .006$, respectively),

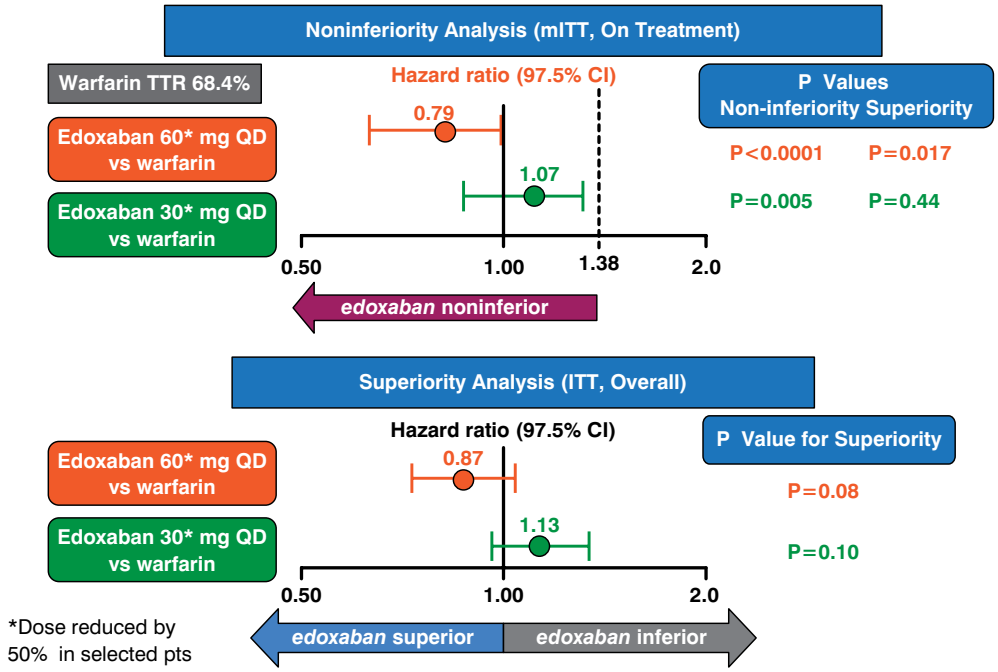
Figure 1. Study Design



CrCl=creatinine clearance; EP=end point; ISTH=International Society on Thrombosis and Haemostasis; P-gp=P-glycoprotein; SEE=systemic embolic event.

Reproduced with permission from Elsevier from 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(4):635–641.

Figure 2. Primary End Point Analyses



ITT=intention-to-treat; QD=once daily; TTR=time to response.
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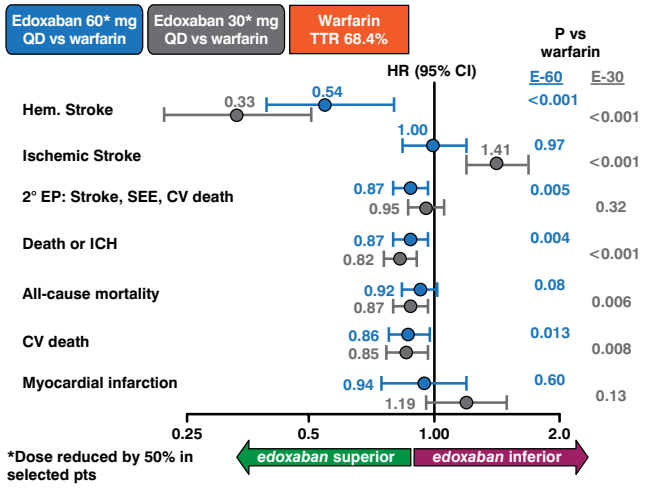
Figure 3. Key Secondary Outcomes



CV=cardiovascular; EP=end point; ICH=intracranial hemorrhage; SEE=systemic embolic event.
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and intracranial hemorrhage ($p < .001$ for both). A dose effect was more apparent for gastrointestinal bleeding, with 30 mg being superior to warfarin ($p = .03$) and 60 mg being inferior ($p < .001$). Edoxaban 30 and 60 mg was superior to warfarin in net clinical outcomes of stroke, systematic embolic events, death, and major bleeding ($p < .001$ and $p = .003$, respectively); disabling stroke, life-threatening bleeding, and death ($p < .001$ and $p = .008$, respectively); and stroke, systematic embolic events, life-threatening bleeding, and death ($p = .007$ and $p = .003$, respectively). Tolerability and the types and occurrence of adverse events were similar for warfarin and both edoxaban doses.

The frequency of hemorrhagic stroke was significantly reduced for both edoxaban doses compared with warfarin: for edoxaban 30 mg, HR .33 (95% CI, .22 to .50; $p < .001$), and for edoxaban 60 mg, HR .54 (95% CI, .38 to .77; $p < .001$). The frequency of ischemic stroke was similar between the warfarin and edoxaban 60 mg arms ($p = .97$) but was significantly elevated in the edoxaban 30 mg arm ($p < .001$).

Because transition from one anticoagulant to another is a high-risk period for patients, the study included a transition plan to protect patients during the transition period from their randomized study drug to open-label anticoagulation. The plan allowed transition to either a vitamin K antagonist (VKA) or a newer oral anticoagulant. If a VKA was selected, frequent early testing of the international normalized ratio was mandated, along

with use of a VKA dosing algorithm and edoxaban-placebo transition kit (which contained matching edoxaban or placebo, depending on whether the patient had been randomly assigned to edoxaban or warfarin during the trial). There were no excess of thrombotic and bleeding events across all 3 study arms during the transition period [Ruff C et al. *J Am Coll Cardiol* 2014].

The trial results indicate the potential value of a once-daily edoxaban regimen, especially using 60 mg, for patients with AF.

GRACE Risk Score Predicts 1-Year Mortality in ACS Patients

Written by Brian Hoyle

Michael Chin, DM, University of the West Indies, Trinidad and Tobago, described the value of the 8-parameter Global Registry of Acute Coronary Events (GRACE) risk score [The GRACE Investigators. *Am Heart J* 2001] in predicting the 1-year mortality of patients discharged with acute coronary syndrome (ACS).

ACS causes about 50% of all cardiovascular-related deaths, and the 1-year survival of ACS patients depends on a variety of patient-related factors and the care received during hospitalization [Lloyd-Jones D et al. *Circulation* 2010]. Management of ACS patients is challenging in a resource-limited setting. Identifying patients at higher risk who may benefit from more aggressive treatment, such as early invasive strategies and coronary care unit monitoring, could help to allocate available resources in an optimal way.

Three risk scores—Thrombosis in Myocardial Infarction, Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using in Tegrilin, and GRACE—are recommended for patient stratification [de Araújo Gonçalves P et al. *Eur Heart J* 2005]. All, especially GRACE, have good predictive accuracy for death and myocardial infarction before discharge and up to 1 year following discharge.

The GRACE investigators previously showed the utility of the GRACE risk score in predicting in-hospital mortality (8.3% of 372 patients) in a multiethnic population in the resource-limited setting of Trinidad and Tobago. The present study analyzed follow-up data in the 341 survivors following hospital discharge to explore whether the GRACE score is valuable in predicting 1-year mortality.

The majority of the patients (n = 207 of 341) were aged > 60 years, and about 72% were of Indian ethnicity. The presenting ACS was categorized as STEMI (ST segment elevation myocardial infarction; 25.2%), non-STEMI (54.3%), and unstable angina pectoris (20.5%).

Figure 1. Baseline Characteristics

Variable	Grace Trinidad (n=372)	Discharge patients (n=341)	Original Grace study (n=11,389)
Mean age	63	62	66.3
Male	57	56.9	66.5
Hypertension	69	69	57.8
Diabetes Mellitus	58	58	23.5
Dyslipidemia	31.2	32.8	43.6
Smoking (Current/Previous)	43	44.6	56.7
Previous Myocardial Infarction	34	34.6	32
Previous CABG	4.6	4.4	12.6
Chronic Kidney disease	6.5	4.4	7.2
Previous PCI	6.7	6.7	14

CABG=coronary artery bypass grafting; PCI=percutaneous coronary infarction.
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The baseline characteristics of patients in the hospitalized and discharged groups in the present study were similar, with both groups differing from the original GRACE study (which predominantly involved Caucasian patients) in terms of the prevalence of diabetes mellitus and hypertension (Figure 1).

The GRACE risk category distribution was fairly even, with high, intermediate, and low risk constituting 30.2%, 34.9%, and 34.9% of the discharged patients, respectively. However, subjects who died were predominantly in the high-risk group (31.5%), compared with the intermediate- (8.3%) and low-risk (3.5%) groups. Predictors of 1-year mortality included age, creatinine, elevated cardiac enzymes, heart rate at admission, Killip class, history of chronic kidney disease, and the GRACE risk score.

The results of the present study extend the utility of the GRACE risk score from a predominantly Caucasian population to patients from a developing (resource-limited) country with a multiethnic population.