stenosis. Secondly, he pointed out that these results should not be applied to other etiologies of RAS including arteritis or firbromuscular dysplasia. He concluded by stating that CORAL showed that renal artery stenting for moderate RAS lesions does not improve clinical outcomes but that the impact of treatment for patients with severe lesions could not be definitively concluded through the CORAL results.

Edoxaban Noninferior to Warfarin in the ENGAGE AF-TIMI 48 Trial

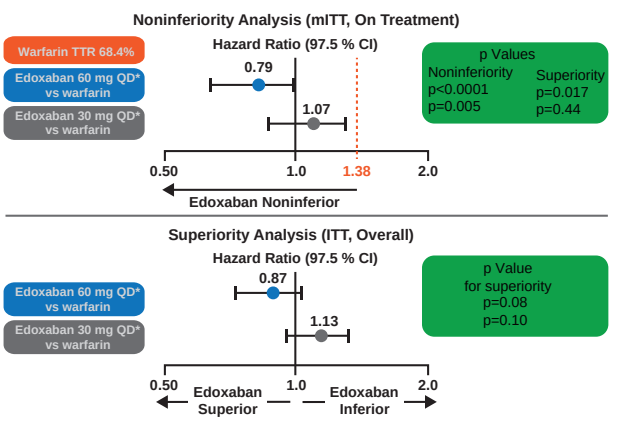
Written by **Muriel Cunningham**

Warfarin is widely used for stroke prevention in patients with atrial fibrillation (AF) but novel oral anticoagulants have been developed that may be just as effective [Dogliotti A et al. *Clin Cardiol* 2013]. Edoxaban is a direct oral factor Xa inhibitor administered once daily with a rapid onset of action. Warfarin and two doses of edoxaban were compared in the Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation – Thrombolysis in Myocardial Infarction 48 study [ENGAGE AF-TIMI 48; Giugliano RP et al. *N Engl J Med* 2013]. This trial enrolled 21,105 patients with AF at moderate to high risk of stroke ($CHADS_2$ ≥2) at 1393 centers in 46 countries. Patients were randomized in a double-blind, double-dummy manner to one of three regimens: 1) warfarin to an international normalized ratio (INR) of 2.0 to 3.0 (n=7036); 2) edoxaban 60 mg/day (high dose; n=7035); or 3) edoxaban 30 mg/day (low dose; n=7034). Edoxaban doses were decreased by 50% if patients had a creatinine clearance of 30 to 50 mL/minute, had a body weight ≤60 kg, or were taking a strong P-glycoprotein inhibitor. The primary endpoint was a composite of stroke or systemic embolic events (SEE). The primary analysis was a noninferiority comparison performed in those patients who took at least one dose of study medications (modified intention-to-treat [mITT] population) during the time that patients were treated (on-treatment time period). Secondary analyses evaluated all patients randomized during the overall treatment period (ITT).

Robert P. Giugliano, MD, Brigham and Women's Hospital, Boston, Massachusetts, USA, presented the primary results from the ENGAGE AF-TIMI 48 trial. Demographic characteristics were well-balanced with no differences between treatment groups in any variable. The median participant age was 72 years (interquartile range, 64 to 78 years), 38% were female, and the mean $CHADS_2$ score was 2.8±1.0. In terms of medical history, 94% had hypertension, 57% had prior congestive heart failure, 36% had diabetes mellitus, and 28% had a prior stroke or transient ischemic attack. A quarter of the patients had an edoxaban dose reduction at randomization.

Over 99% of the patients completed the trial, and only one patient was lost to follow-up. Overall the median time in the therapeutic range was 68.4% (interquartile range, 56.5 to 77.4). The primary endpoint was based on a median follow-up of 2.8 years. Both doses of edoxaban met the noninferiority criteria (p<0.0001 for high-dose edoxaban and p=0.005 for low-dose ; Figure 1) in the mITT population while on treatment. Neither edoxaban regimen was statistically superior for the primary endpoint (p=0.08 for high dose and p=0.10 for low dose in the ITT analysis during the overall time period; Figure 1). Both doses of edoxaban had significant reductions in key secondary outcomes (Figure 2) and safety endpoints (Figure 3).

Figure 1. Primary Endpoint Results



Both dose regimens of edoxaban were noninferior to warfarin in the primary noninferiority analysis. The high-dose regimen tended to be more effective at reducing stroke/SEE compared with warfarin and the low-dose regimen less effective.

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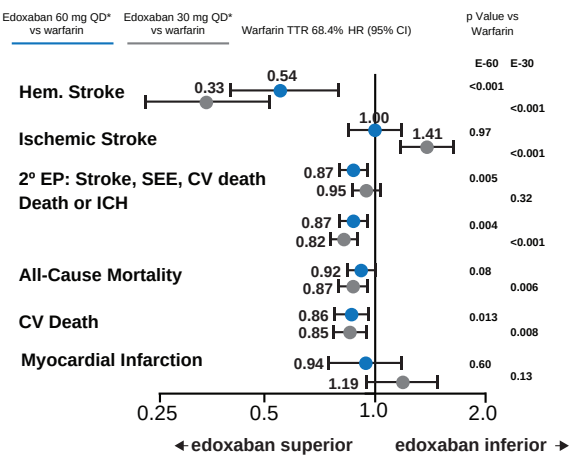
Figure 2. Secondary Endpoint Results



Both dose regimens of edoxaban reduced hemorrhagic stroke, death or ICH, and CV death compared with warfarin. The low-dose regimen was not as effective as warfarin at reducing ischemic stroke. CV=cardiovascular; E-60=edoxaban 60 mg QD dose group; E-30=edoxaban 30 mg QD dose group; ICH=intracerebral hemorrhage; SEE=systemic embolic events, TTR=time in therapeutic range.

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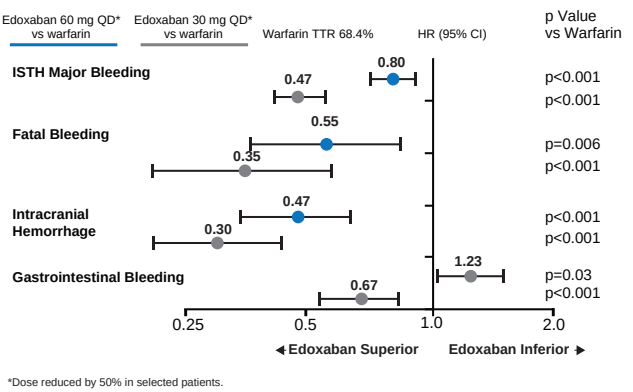
Figure 3. Key Safety Results



*Dose reduced by 50% in selected patients. Both dose regimens of edoxaban substantially reduced major, fatal, and intracranial bleeding. Gastrointestinal bleeding was increased with high-dose edoxaban compared with warfarin, but reduced with the low-dose regimen compared with warfarin. TTR=time in therapeutic range.

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Both edoxaban regimens were well tolerated and no significant differences were observed in serious adverse events or liver abnormalities compared with warfarin. In terms of net clinical outcomes, both the high-dose and low-dose edoxaban regimens led to significant reductions in composite endpoints of stroke/SEE/death/major bleeding (p=0.003 and p<0.001, respectively), disabling stroke/life-threatening bleeding/death (p=0.008 and p<0.001, respectively), and stroke/SEE/life-threatening bleeding/death (p=0.003 and p=0.007, respectively).

In this large, randomized, controlled international trial, once-daily edoxaban was noninferior to well-managed warfarin for the prevention of stroke and SEE, with a trend toward fewer stroke/SEEs observed with the higher dose. Both edoxaban regimens had superior net clinical outcomes, which assessed various combinations of death, stroke, and bleeding events, compared with warfarin.

Immediate Targeted Blood Pressure Reduction Does Not Improve Outcomes in Acute Stroke

Written by Nicola Parry

Jiang He, MD, PhD, Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana, USA, presented the final results from the China Antihypertensive Trial in Acute Ischemic Stroke [CATIS; He J et al. *JAMA* 2013] trial, demonstrating that in acute ischemic stroke patients with elevated blood pressure (BP), antihypertensive treatment to reach a lower target BP does not reduce their risk for death or disability within 14 days.

CATIS was a multicenter, randomized trial, designed to evaluate whether immediate BP reduction to a BP target, within 48 hours of symptom onset, in patients with acute ischemic stroke would reduce morbidity and mortality compared with allowing hypertension during the acute hospitalization.

Inclusion criteria included age ≥22 years, ischemic stroke onset within 48 hours confirmed by imaging (computed tomography or magnetic resonance imaging), systolic BP (SBP) ≥140 and <220 mm Hg and diastolic BP (DBP) ≥80 mm Hg, and no contraindications to antihypertensive therapy Patients with severe heart failure, acute coronary syndrome, aortic dissection, atrial fibrillation, cerebrovascular stenosis, resistant hypertension, and those in a deep coma were excluded, as were individuals receiving intravenous thrombolytic therapy.

The primary endpoint of the study was a combination of death and major disability within 14 days, or at the time of discharge, if that occurred prior to 14 days. The secondary outcome was a composite of all-cause mortality and major disability (a score of 3 to 5 on the modified Rankin Scale) over 3 months of follow-up.

A total of 4071 patients were randomized to either antihypertensive treatment to reduce SBP by 10% to 25% within the first 24 hours after randomization and then to a target BP <140/90 mm Hg within 7 days to be maintained during the hospitalization (n=2038) or no antihypertensive treatment during hospitalization (n=2033). At baseline, the mean age of study participants was 62.0 years, and 64.0% were men. Stroke severity was similar in both groups, as assessed using the National Institutes of Health Stroke Scale (median score 4.0). The mean time from onset of ischemic stroke to randomization was 15.3 and 14.9 hours in the treatment and control groups, respectively; mean systolic BP at entry was 166.7 and 165.6 mm Hg, and mean diastolic BP was 96.8 and 96.5 mm Hg.

Various antihypertensive agents were used in the treatment group, including intravenous angiotensin-converting enzyme inhibitors (enalapril, first-line), calcium channel blockers (second-line), and diuretics (third-line).

Within 24 hours, mean SBP decreased by an average of 12.7% in the treatment group, and 7.2% in the control group (difference, –5.5%; 95% CI, –4.9 to –6.1; p<0.001). And by Day 7, mean SBP was 137.3 mm Hg in the treatment group, and 146.5 mm Hg in the control group (difference, –9.3 mm Hg; 95% CI, –10.1 to –8.4; p<0.001). However, at 14 days or hospital discharge, there was no significant difference in primary outcome between the treatment and control groups (683 vs 681 events; OR, 1.00; 95% CI, 0.88 to 1.14; p=0.98; Table 1).