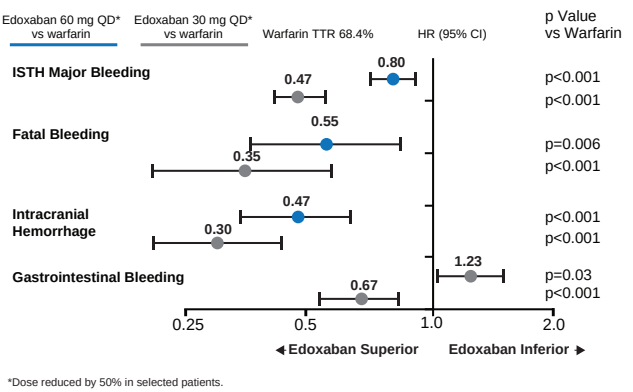
Figure 3. Key Safety Results



*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).

Table 1. CATIS Primary and Secondary Endpoints at 14 Days

	Treatment	Control	Odds Ratio (95% CI)	p Value
Death or major disability, %	33.6	33.6	1.00 (0.88, 1.14)	0.98
Median modified Rankin score	2.0	2.0		0.70
Death, %	1.2	1.2	1.00 (0.57, 1.74)	0.99
Median time of hospitalization, days	13.0	13.0		0.28

Similarly, there was no significant difference in the secondary composite outcome of death and major disability at 3-month post-treatment follow-up (500 vs 502 events; OR, 0.99; 95% CI, 0.86 to 1.15; p=0.93; Table 2).

Table 2. CATIS Secondary Outcomes at 3-Month Follow-Up

	Treatment	Control	Odds Ratio (95% CI)	p Value
Death or major disability, %	25.2	25.3	0.99 (0.86, 1.15)	0.93
Median modified Rankin score	1.0	1.0		0.52
Death, %	3.4	2.7	1.27 (0.88, 1.82)	0.20
Recurrent stroke, %	1.4	2.2	0.65 (0.40, 1.04)	0.07
Vascular events, %	2.4	3.0	0.81 (0.55, 1.19)	0.28
Death or vascular events, %	4.6	4.7	0.98 (0.73, 1.31)	0.88

Dr. He concluded that, in hypertensive acute ischemic stroke patients, unless BP is very high (≥220/120 mm Hg), routine use of antihypertensive treatment to rapidly reduce BP to 140/90 mm Hg does not reduce morbidity or mortality.

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