MRI Guided Thrombolysis for Stroke with Unknown Time of Onset (The WAKE UP Trial)

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IV TPA is standard of care for acute ischemic stroke within the first 4.5 hours of symptom onset, however in up to 27% of strokes the symptom onset is unknown, particularly when a patient wakes from sleeping with stroke symptoms. Additionally in patients with known symptom onset, a DWI hyperintense lesion on MRI with corresponding lack of FLAIR hyperintensity (DWI/FLAIR mismatch) is predictive of the ischemic lesion of occurring within 4.5 hours. This study was performed to evaluate the safety and efficacy of IV TPA in patients with unknown time of symptoms onset with DWI/FLAIR mismatch on MRI.

Methods: This was a Randomized, double-blinded, placebo-controlled multicenter clinical trial, performed in 70 centers across 8 European countries. Both local investigators and a central image-review committee screen patients for eligibility. Patients were eligible for inclusion if they presented with clinical signs of acute stroke, age 18-80 years, had been able to complete activities of daily living prior to stroke, LKW > 4.5 hours prior to presentation (could be LKW prior to awakening OR unknown/unreportable LKW). Their MRI had to have DWR/FLAIR mismatch. Patients were excluded if they presented within 4.5 hours of LKW (were within the standard tPA window), had hemorrhage on MRI, had lesions larger than 1/3 the territory of the MCA, had NIHSS >25, had a planned thrombectomy, or had contraindication to TPA (other than time window). Patients randomized in 1:1 ratio to placebo or standard dose IV TPA. Primary outcome was favorable outcome, defined as MRS 0-1, at 90 days. Primary safety end points were death and a composite outcome of death or dependence (score of 4-6 on MRS at 90 days), secondary safety endpoints were symptomatic ICH and incidence of parenchymal hematoma type 2 (blood exceeding 30% of infarct area). Data was analyzed on an intention-to-treat basis. The study was stopped early due to lack of funding.

Results: 503 patients were randomized, 254 received alteplase and 249 received placebo. The characteristics of the 2 groups were similar at the start of the trial, except for a higher rate of intracranial ICA occlusion in the alteplase group. Treatment with tPA was associated with a favorable outcome in 53.3% of the treatment group vs. 41.8% of the placebo group. (OR 1.61; 95% CI 1.09-2.36; P=0.02). Death at 90 days in the tPA group occurred in 4.1% vs. 1.2% in the placebo group (Adjusted OR 3.38; 95% CI 0.92 to 12.52; P=0.07). In the TPA group death or dependency (MRS 4-6) occurred in 13.5% vs. 18.3% (Adjusted OR 0.68; 95% CI 0.39 to 1.18; P=0.17). There was significantly higher Intraparenchymal hemorrhage type 2 in the TPA group (4.0% vs. 0.4%, Adjusted OR 10.46; 95% CI 1.32 to 82.77; P=0.03). There was numerically higher symptomatic ICH in the TPA group, accounting for multiple definitions of “Symptomatic ICH” from prior trials.

Conclusions: The trial found that in patients with an unknown time of stroke onset with DWI/FLAIR mismatch on MRI who are treated with IV TPA have significantly improved functional outcomes without a significantly increased risk of death disability. There was an increased rate of ICH that was similar to prior TPA trials. This trial has led to the wake up MRI based protocols at many centers. There were few patients with NIHSS <10, so it is unclear if the results are generalizable to that group. Since the trial ended early due to lack of funding, not enough patients were enrolled to power any subgroup analysis. There was a numerically higher number of deaths in the TPA group that neared, but did not reach, significance; this may have reached significance if the trial had the funding to enroll the target number of patients. Patients pre-determined to receive thrombectomy were excluded, and 20% of patients in

the trial would have qualified for DAWN or DEFUSE 3, it is unclear if this group of patients would have greater benefit from thrombectomy, IV TPA, or both.

Summary Complied by Nathan Bicher, MD