The study also found no superior benefit with embolectomy over standard care based on imaging pattern. Outcomes of embolectomy and standard care were a mean 90-day mRS score of 3.9 versus 3.4, respectively (p=0.23), for patients with a favorable penumbral pattern and a mean score of 4.0 versus 4.4, respectively (p=0.38), for patients with a nonpenumbral pattern. According to Dr. Kidwell, the study underscores the importance of confirming hypotheses in randomized, controlled trials prior to implementing treatment approaches in clinical practice.

MISTIE II Trial: 365-Day Results Demonstrate Improved Outcomes and Cost Benefit

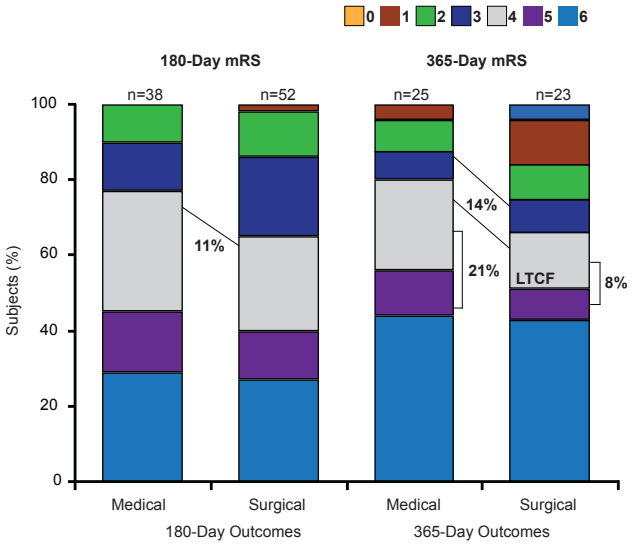
Written by **Phil Vinall**

Daniel Hanley, MD, Johns Hopkins University, Baltimore, Maryland, USA, presented results from the Minimally Invasive Surgery Plus tPA for Intracerebral Hemorrhage Evacuation trial [MISTIE; NCT00224770], which showed that catheter-based clot reduction plus tissue plasminogen activator (MIS + tPA) is safe and may reduce long-term disability after intracerebral hemorrhage.

Volume of intracerebral hemorrhage (ICH) is the strongest predictor of 30-day outcome for all locations of spontaneous ICH [Broderick JP et al. *Stroke* 1993]. MISTIE was a 2-stage multicenter, Phase 2 trial that examined outcomes and cost benefit of reducing clot size by using a catheter inserted into the largest part of the clot to apply tPA every 8 hours for 3 days. The study included patients with spontaneous supratentorial ICH ≥20 cc (stable ≥6 hours post diagnosis as shown on computed tomography) who were treated with either MIS plus tPA (n=54) or standard medical care (n=42) and followed for 180 days for stage I and 365 days for stage II. Participants were mean age 61 years (55.2% white, 65.6% men). Most were hypertensive (86.5%) and 26.5% had a diagnosis of diabetes. Prior smokers were more common in the surgical group (31.5%) versus those receiving standard medical therapy (7.1%). Of the subjects, 75% received their surgery between 12 and 38 hours post event.

At 365 days there was a 14% difference in functional performance (defined as 0 to 3 vs 4 to 6 on the modified Rankin Scale [mRS]) favoring MIS plus tPA (slightly greater than the 11% difference observed at 180 days). The improvement included a differential shift to higher independence levels at mRS 0 to 2 (Figure 1). Similar magnitudes of improvement (Figure 2) were also seen when the subjects were evaluated for improvements in mobility and activities of daily living using the Stroke Impact Scale [Duncan PW et al. *Stroke* 1999].

Figure 1. Functional Outcomes



LTCF=long-term care facility; mRS=modified Rankin Scale.

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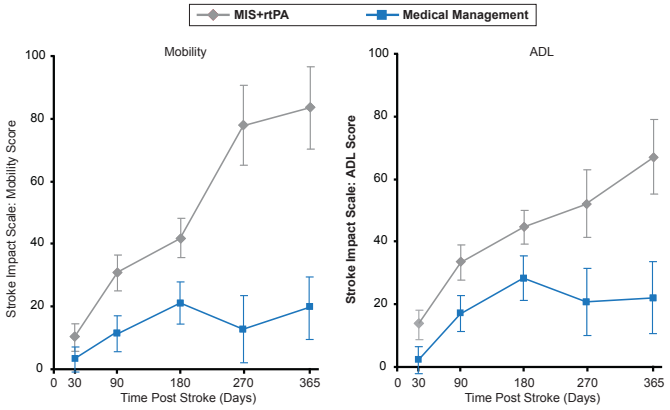
Figure 2. Functional Improvements: Stroke Impact Scale



ADL=activities of daily living; MIS=minimally invasive surgery; rtPA=recombinant tissue plasminogen activator.

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The improvements were also reflected in the cost of care. Although the median length of intensive care unit (ICU) stay was similar for both groups (9 days for patients in the surgical group vs 8 days for patients in the standard medical therapy group) the median hospital stay was 38 days shorter for the MIS plus tPA group (p=0.015). In addition, fewer surgical patients were residing in long-term care facilities both at 180 (17% vs 24%; not significant) and 365 days (8% vs 21%; not significant). After accounting for all costs (eg, ICU stay, MIS + tPA procedures), the results indicate that the experimental procedure saves an estimated $44,329 of medical care costs per patient [Hanley DF et al. ISC 2013 (abstr LB1)].

Similar results were obtained for all subgroups. Importantly, the treatment effect does not seem to be mitigated by the depth or size of the hematoma or the time to surgery. There is a progressive improvement in mRS outcomes as the amount of clot removed is increased.

Dr. Hanley believes that reduction in clot burden is a mechanism of benefit, MIS plus tPA saves tissue at risk, and secondary injury occurs over days—not just immediately. "Most likely MIS plus tPA increases independence and appears to improve function and decrease cost," he said. This procedure needs to be tested in a large Phase 3 trial.

Addition of AMPLATZER PFO Occluder to Medical Therapy Is Beneficial in Patients With Cryptogenic Stroke and PFO

Written by **Emma Hitt, PhD**

Cryptogenic stroke remains a major challenge for clinicians taking care of patients who have had strokes. Patent foramen ovale (PFO) is a contributor to cryptogenic stroke due to paradoxical embolism [Furlan AJ et al. *N Engl J Med* 2012], but the optimal management strategy for PFO has yet to be defined [Kitsios GD et al. *Stroke* 2012]. Jeffrey L. Saver, MD, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, USA, reported the results of a follow-up analysis of the RESPECT PFO Clinical Trial [RESPECT; NCT00465270] to characterize the qualifying and endpoint ischemic strokes.

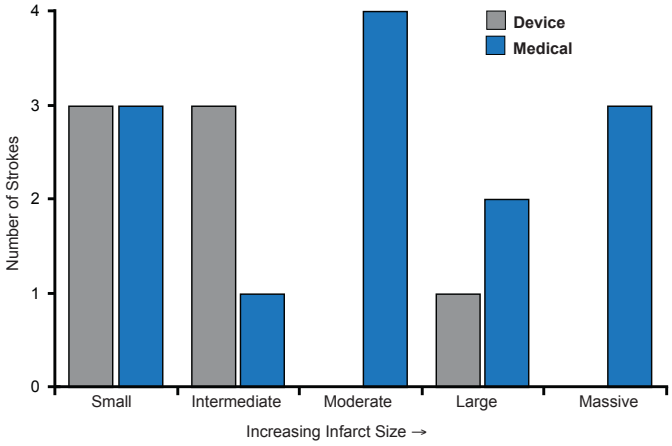
RESPECT included patients aged 18 to 60 with PFO who had a cryptogenic stroke within 270 days. Enrollment continued until the 25th endpoint. Patients were randomized to the device group (n=499) or the medical group (n=481). The device group received closure with the AMPLATZER PFO Occluder plus medical therapy, and the medical group was scheduled to receive 1 of 5 medical treatment regimens (aspirin, warfarin, clopidogrel, or aspirin with dipyridamole); however the fifth treatment regimen of aspirin with clopidogrel was removed from the protocol as it was no longer included in the American Heart Association/American Stroke Association treatment guidelines.

Patients were excluded from the trial if they had cerebral, cardiovascular, and/or systemic conditions that suggested mechanisms other than PFO were responsible for the stroke. These mechanisms included atrial fibrillation, carotid disease, cardiomyopathy, small artery disease, uncontrolled diabetes mellitus or hypertension, arterial hypercoagulable states, or other sources of right-to-left shunt.

Primary analysis of the trial has previously shown that there was a 46.6% to 72.7% reduction in risk of stroke in the device versus the medical therapy group [Carrol JD. TCT 2012]. In the follow-up analysis, the basic features of the stroke patients were similar in the device and medical groups. The topography and lesion size of the qualifying strokes were also well balanced between the 2 groups. There was a trend towards magnified value of the device compared with the medical group in patients whose qualifying events occurred in the setting of atrial septal aneurysms (p=0.016), a large shunt size (p=0.012), or in an isolated superficial distribution (p=0.049).

The topography of endpoint ischemic strokes was significantly different between the medical and device groups. The medical group had a larger proportion of strokes that were superficial, mixed superficial and deep, or otherwise not small and deep in distribution compared with the device group (p=0.04). In addition, the medical group experienced more infarcts ≥1.5 cm (69.2%) than the device group (14.3%; p=0.06). Figure 1 shows a general shift towards larger lesion size in the medical group compared with the device group.

Figure 1. Lesion Size of Endpoint Ischemic Strokes



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Limitations of the RESPECT trial include the limited power of the subgroup interaction analysis with only 25 events to explore. In addition, the work-up of endpoint events was incomplete in some cases since some strokes were evaluated at nonstudy centers, and all patients had already had a complete evaluation for qualifying infarcts, so not all tests were repeated in every patient.

Dr. Saver said, "Consideration of the neurovascular aspects of the RESPECT trial reinforce the primary analysis." When patients were stringently selected to identify those with a history of cryptogenic stroke and PFO, closure with the AMPLATZER PFO Occluder showed evidence of benefit over medical management alone. The device was more effective at averting infarcts associated with a paradoxical