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.

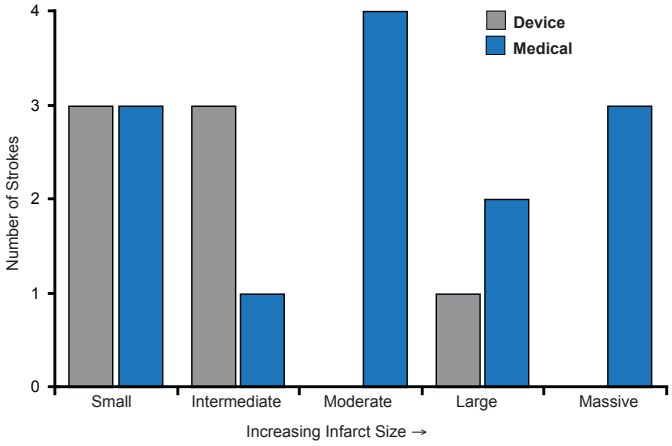
RESPECT included patients aged 18 to 60 with PFO who had a cryptogenic stroke within 270 days. Enrollment continued until the 25th endpoint. Patients were randomized to the device group (n=499) or the medical group (n=481). The device group received closure with the AMPLATZER PFO Occluder plus medical 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

embolic stroke mechanism, including those with superficial vascular distribution, convexity strokes, and strokes of larger size, providing additional evidence of a biological effect of closure with the AMPLATZER PFO Occluder.

Intraoperative CT-Guided Endoscopic Surgery for ICH [ICES]

Written by **Phil Vinall**

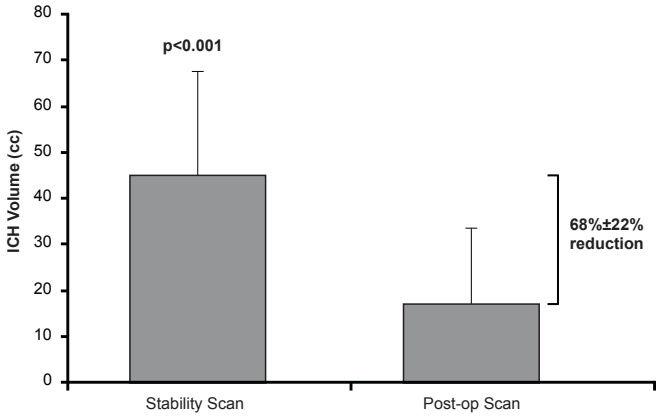
Paul Vespa, MD, University of California, Los Angeles, Los Angeles, California, USA, presented 180-day data from the Intraoperative CT-Guided Endoscopic Surgery trial [ICES] showing that early CT-guided endoscopic surgery is safe and associated with improved neurological outcomes compared with medical management in patients with primary intracerebral hemorrhage (ICH).

ICES is a substudy of the Minimally Invasive Surgery Plus rtPA for Intracerebral Hemorrhage Evacuation study [MISTIE; NCT00224770]. The inclusion and exclusion criteria for ICES were the same as for MISTIE to facilitate a prespecified comparison between ICES surgery and the combined ICES plus MISTIE medical control arm. Randomization and surgery took place within 48 hours of stroke onset. Two serial CT scans were performed ≥6 hours apart to ensure that the hematoma remained stable. The ICH volume threshold was >20 cc; some intraventricular hemorrhage was permitted.

Surgery was accomplished using a stereotactic navigational scan. The endoscope was inserted two thirds of the way into the hematoma along its long axis, and suction and then irrigation were applied for variable amounts of time. The endoscope was backed off to about one third of the depth, and suction and irrigation were repeated before the instrument was withdrawn. A postoperative CT scan was performed. The primary study endpoint was safety. Secondary endpoints included volume reduction, surgical serious adverse events, and modified Rankin Scale (mRS) score at 180 and 365 days.

Subjects (mean age, ~62 years; mostly men) were randomly assigned to endoscopic surgery (n=18) or medical management (n=6). Mean time to surgery was 32.8±14 hours. Endoscopic surgery resulted in a 68%±22% immediate volume reduction (p<0.001; Figure 1) with the volume being reduced to <15 cc in 67% of patients. Volume was unchanged in the medically managed patients after 72 hours. Mortality at 7, 30, and 180 days post onset was significantly higher in the medical (0%, 7%, and 60%, respectively) versus the surgical arm (0%, 4%, and 13%, respectively; p<0.01). One surgical patient had immediate nonfatal postoperative rebleeding. There was no immediate surgical-related mortality.

Figure 1. Volume Reduction



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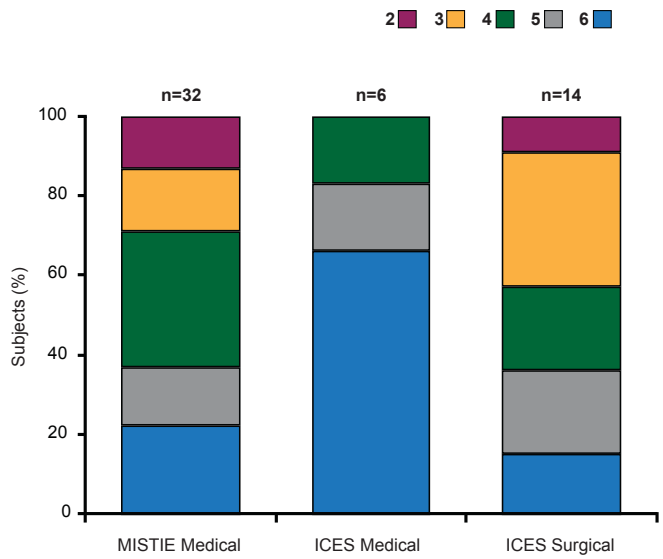
At 180 days, good neurological outcome (mRS score 0 to 3) was more frequent in patients receiving surgery (45%) compared with those on medical therapy (0%; Figure 2). On a prespecified intention-to-treat secondary analysis of ICES surgery versus combined medical controls in ICES plus MISTIE (n=13 vs n=36) at 180 days, the proportion of mRS scores 0 to 3 remained 15% greater in ICES surgery versus combined medical controls (38% vs 23%) [Vespa P et al. ISC 2013 (abstr LB2)].

Figure 2. Functional Outcomes: mRS at Day 180



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