confirm that successful recanalization is associated with better clinical outcome. This study also shed some light on the effect of intubation, procedure duration, and time to treatment on clinical outcome. However, this analysis was based on nonrandomized, self-reported data in the absence of a control. Therefore, efficacy of this treatment approach compared with standard medical therapy was not addressed by this study, and further randomized controlled studies are warranted.

Perlecan Domain V is a Novel Stroke Treatment

Perlecan domain V (DV) may improve functional stroke outcome. Boyeon Lee, PhD, Texas A&M College of Medicine, College Station, TX, presented findings from a study that investigated the effect of the extracellular matrix (ECM) fragment perlecan domain V on angiogenesis and neurogenesis in poststroke rats and mice.

Neurovascular coupling of angiogenesis and neurogenesis has been shown to involve ECM remodeling and ECM fragment initiation [Ohab JJ et al. *J Neuroscience* 2006]. Additionally, DV has been shown to interact with the ECM and promote angiogenesis [Segev A et al. *Cardiovasc Res* 2004; Mongiat M et al. *J Biol Chem* 2003]. In this study by Lee and colleagues, sham surgery control was performed or transient middle cerebral artery occlusive stroke was induced by using sterotactic injection of endothelin-1 in rats or tandem ipsilateral common carotid artery and middle cerebral artery occlusion in mice. All subjects received either intraperitoneal injections of human recombinant DV 0.5-1 mg/kg or phosphate-buffered saline control at Days 1, 3, 5, and 7 poststroke (n=15 for each group). Functional use of the affected limb was determined by the vibrissae-elicited paw placement reflex in mice and the cylinder test in rats. Concurrent brain microvascular endothelial cell *in vitro* studies were also performed to evaluate the effect of DV on angiogenesis.

Brain immunohistochemistry (von Willebrand factor) demonstrated that perlecan DV homed to the stroke and peri-infarct vasculature. DV was significantly higher in the stroked cerebral hemisphere at Days 1, 3, 5, and 7 poststroke compared with corresponding contralateral hemisphere levels (Day 1 p=0.0001; Day 3 p=0.0007; Day 5 p=0.007; Day 7 p=0.005). Additionally, subjects that were treated with DV had more neurons with normal morphology and lower incidence of TUNEL-positive cells or shrunken and misshapen cells, suggesting a neuroprotective component that was associated with DV. DV treatment was associated with increased poststroke neurogenesis and poststroke angiogenesis. Significant increases were observed in stroke peri-infarct vasculature in subjects that were treated with DV on poststroke Days 3, 5, and 7 versus control (p=0.001; p<0.00001; p<0.00001 for Days 3, 5, and 7, respectively). DV treatment also resulted in significantly more doublecortin-positive pixels on poststroke Days 3, 5, and 7 versus control (Day 3, p=0.00001; Day 5, p<0.00001; Day 7, p<0.00001, resulting in enhanced poststroke neurogenesis.

Functional stroke outcome was significantly better in stroked subjects that were treated with DV versus control, and improvement in contralateral paw use was observed at Days 3 (p=0.03) and 7 (p=0.009) poststroke. While significant contralateral forelimb improvement was noted in those that were treated with DV, PBS control subjects remained significantly impaired at poststroke Days 3 (p=0.008), 5 (p=0.006), and 7 (p=0.005).

The *in vitro* analysis that was included in this study revealed possible mechanisms by which DV affects angiogenesis. At 3 days poststroke, an increase in α5β1 levels was noted in those that were treated with DV. DV enhances brain endothelial cell formation, which may be inhibited via α5β1. In α5β1 and DV coimmunohistochemistry of brain endothelial cells, colocalization of DV and α5β1 was identified. DV also induces brain endothelial cell VEGF synthesis and release via the α5β1 integrin. A DV dose-dependent VEGF response was noted *in vitro*.

Dr. Lee concluded that DV is neuroprotective and promotes poststroke angiogenesis and neurogenesis, thus, contributing to improved functional stroke outcome. DV-induced VEGF release via the α5β1 integrin pathway plays a role in the DV angiogenesis and neurogenesis. However, the extent of their involvement remains unclear. Results from this study are promising and suggest that perlecan DV may provide a viable treatment option for stroke in the future.

Failure to Validate Association Between Variants on 12p13 and Ischemic Stroke

A meta-analysis of genomewide association studies (GWAS) did not validate findings that associated the single-nucleotide polymorphisms rs12425791 and rs11833579 with stroke. Representing the members of the International Stroke Genetics Consortium, Jonathan Rosand, MD, MSc, Massachusetts General Hospital, Boston, MA, detailed findings from this meta-analysis.

A previous GWAS found that two intergenic single-nucleotide polymorphisms (SNPs), rs12425791 and

rs11833579, on chromosome 12p13 and within 11 kb of the NINJ2 gene were associated with stroke [Ikram MA et al. *N Engl J Med* 2009]. The International Stroke Genetics Consortium set out to validate these results in a meta-analysis that was conducted using a combined sample of 8637 cases and 8733 controls of European ancestry and one population-based genomewide cohort study of 278 ischemic strokes among 22,054 subjects. Investigators evaluated associations between the two SNPs and ischemic stroke, incident stroke, and stroke subtypes (according to Trial of ORG 10172 in Acute Stroke Treatment [TOAST] criteria). Similar analyses were performed in cases and controls of African-American, Pakistani, and Chinese ancestry.

This well-powered meta-analysis detected no association between rs12425791 or rs11833579 and ischemic stroke in the cohort of European ancestry (OR, 0.97; 95% CI, 0.91 to 1.04; p=0.41 and OR, 1.02; 95% CI, 0.95 to 1.10; p=0.55, respectively). Additionally, no association was found for atherothrombotic stroke, incident ischemic stroke, recurrent ischemic stroke, or any of the ischemic stroke subtypes with regard to either SNP, according to 2235 cases (p>0.10 for all stroke categories). The original meta-analysis reported significant heterogeneity (rs11833579: heterogeneity p=0.073, I2=56.1%; rs12425791: p=0.15, I2=42.1%). However, no significant heterogeneity was observed in the current meta-analysis by the consortium (heterogeneity p>0.20; I2<20%).

Based on these results, members of the International Stroke Genetics Consortium concluded that these SNPs were not associated with increased risk for ischemic stroke.

Results from the Penumbra Pivotal Stroke Trial Substudy

While the Penumbra Pivotal Stroke Trial demonstrated a recanalization rate of 81.6%, the rate of good clinical outcome, defined as a modified Rankin Scale (mRS) score ≤2, was relatively low (25%) [The Penumbra Pivotal Stroke Investigators. *Stroke* 2009]. Mayank Goyal, MD, University of Calgary, Calgary, Alberta, Canada, presented a subanalysis from the Penumbra Pivotal Stroke Trial.

The aim of this substudy was to evaluate whether a good initial noncontrast computed tomography (NCCT), defined as >7 according to the ASPECTS scoring system, and short time to recanalization predicted good clinical outcome in patients with acute ischemic stroke who were undergoing endovascular procedures. The substudy included 85 of the original 125 Penumbra trial participants (median age 64.1 years), stratified by blinded NCCT reading at presentation. Patients were grouped according to NCCT ASPECTS score of >7 or ≤7 (median ASPECTS score at baseline was 6). ASPECTS scores were categorized as good (8 to 10; observed in 36.5% of patients), intermediate (5 to 7), and poor (0 to 4). The primary outcome was mRS ≤2 at 3 months.

Medical comorbidities at baseline included hypertension (n=83), diabetes (n=23), and atrial fibrillation (n=34). Occlusions were located in the internal carotid artery in 22.4% of patients (19.3% had ASPECTS scores >7 vs 24.1% ≤7), in the M1 main coronary artery in 63.5% of patients (61.3% had ASPECTS scores >7 vs 64.8% ≤7), and in the M2 main carotid artery in 14.1% of patients (19.3% had ASPECTS scores >7 vs 11.1% ≤7) at baseline.

TIMI scores of 2 to 3 were noted in 81.2% of patients. Of the patients with ASPECTS scores >7, 83.9% had TIMI 2 to 3 recanalization compared with 79.6% with ASPECTS scores ≤7 (p= 0.8). At 3 months, mRS 0 to 2 was observed in 27.1% of patients, 50% in the ASPECTS scores >7 group, and 15% in the ASPECTS scores ≤ 7 group (Table 1). When broken down by ASPECTS categories of good, intermediate, and poor, good clinical outcome was significantly greater in the >7 group compared with the ≤7 group (RR 3.3; 95% CI, 1.6 to 6.8; Table 1), and no patient with an ASPECTS score ≤4 (poor scan, n=28) had good clinical outcome. Additionally, good clinical outcome was significantly higher in the early recanalizer (≤300 minutes) group compared with the combined late recanalizer (>300 minutes) or nonrecanalizer (TIMI 0 to 1) group (RR 2.3; 95% CI, 1.2 to 4.4). No patient without recanalization (TIMI 0 to 1; n=16) did well.

Table 1. Clinical Outcomes Stratified by Baseline CT ASPECTS Score.

	Total (n=85)	ASPECTS >7 (n=31)	ASPECTS ≤7 (n=54)	p value
TIMI (2 to 3)	81.2%	83.9%	79.6%	0.8
Median Onset to Recanalization (time in minutes)	365.5	390	359	0.6
mRS (0 to 2) at 90 days	27.1%	50%	15%	0.001

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After adjusting for baseline stroke severity, there was evidence of an ASPECTS score and onset-to-recanalization time interaction. The direction of interaction was such that among patients with ASPECTS scores >7, the relative effect of onset-to-recanalization time (≤300 minutes or >300 minutes) in predicting outcome was small. Among patients with ASPECTS scores ≤7, only those with an onset-to-recanalization time ≤ 300 minutes had some chance of achieving a functional outcome (Figure 1).