life were observed when the intervention arm was compared with the control arm.

Additional subgroup analyses favored intervention across all groups including patients over the age of 80 years. The investigators concluded that endovascular thrombectomy is a safe intervention, reducing mortality and disability when patients are carefully selected using imaging, when treatment is administered very quickly, and when safe, effective technology, such as retrievable stents, is employed.

CADISS Revealed Low Recurrent Stroke Rate in Patients With Cervical Artery Dissection

Written by Alla Zarifyan

Hugh S. Markus, BM Bch, University of Cambridge, Cambridge, United Kingdom, presented the first results of the Cervical Arterial Dissection in Stroke Study (CADISS) trial [ISRCTN44555237]. The CADISS trial demonstrated that the recurrent stroke rate due to cervical artery dissection appears to be low, with no significant difference in outcome by using antiplatelet vs anticoagulant treatment for future stroke prevention. Investigators also determined that the number of patients needed to show a difference between treatment arms was high and could be challenging to obtain.

Carotid and vertebral dissection is an important cause of stroke in young and middle-aged patients, accounting for up to 25% of cases [Beletsky V et al. *Stroke*. 2003; Touzé E et al. *Neurology*. 2003]. It carries an associated risk of recurrent stroke, although the reported numbers vary widely, depending on the study reviewed. Physicians usually prescribe either anticoagulation or antiplatelet agents to prevent recurrent strokes; however, data from randomized controlled trials showing the superiority of one treatment over another are currently lacking, with some nonrandomized data providing inconclusive results [Kennedy F et al. *Neurology*. 2012].

CADISS was a randomized, open-label trial, with blinded adjudication of end points [Markus HS et al. *Int J Stroke*. 2007]. The primary aim was to determine whether antiplatelet vs anticoagulation treatment was more effective at preventing stroke in patients with acute cervical dissection. The secondary aim was to measure the frequency of recurrent stroke in this population. Initially, 250 patients were recruited in order to establish whether there would be a sufficient number of clinical end points to determine a treatment effect, and if an adequate number of patients can be feasibly recruited. The primary end point was ipsilateral stroke or death at 3 months. Eligible patients had to have symptoms of ipsilateral stroke or transient ischemic attack, or ipsilateral Horner syndrome, neck pain, or headache within 7 days of recruitment.

Out of 250 patients, 126 were randomized to antiplatelets and 124 to anticoagulants. End points included 4 ipsilateral strokes (all in patients presenting with stroke; 3 in antiplatelet group and 1 in anticoagulant group) and 1 subarachnoid hemorrhage (in anticoagulant group). No deaths were reported. The overall stroke rate was strikingly low at 1.6% (2.1% in those presenting with stroke or transient ischemic attack). Given the low number of events, the difference between treatment arms was not significant (Table 1).

A predefined per-protocol analysis was also performed after excluding patients whose diagnosis of dissection could not be confirmed by reviewing their imaging data. Overall, 53 patients were excluded. The per-protocol analysis included 197 patients. There were 3 per-protocol end point events (defined as stroke, major bleeding, or death) among 101 patients in the antiplatelet group and 2 among 96 patients in the anticoagulant group (Table 2), with insignificant difference between treatment arms.

Table 1. Association Between Treatment and Risk of End Point Event in ITT Population

	Anticoagulants, n (%) (n = 124)	Antiplatelets, n (%) (n = 126)	OR	95% CI	*P* Value
Ipsilateral stroke or death	1 (0.8)	3 (2.4)	0.335	0.006 to 4.233	.63
Any stroke, death, or major bleeding	2 (4.0)	3 (3.2)	0.673	0.055 to 5.983	1.00
Any stroke	1 (0.8)	3 (2.4)	0.335	0.006 to 4.233	.63
Ipsilateral stroke, TIA, or death	5 (4.0)	4 (3.2)	1.280	0.268 to 6.614	.98
Any stroke, TIA, or death	5 (4.0)	5 (4.0)	1.017	0.228 to 4.540	1.00

ITT, intent to treat; TIA, transient ischemic attack.

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Table 2. Incidence of End Point Events by Treatment in Per-Protocol Population

	Antiplatelets (n = 101)	Anticoagulants (n = 96)
Ischemic stroke		
Ipsilateral	3	1
Other	0	0
TIA		
Ipsilateral	1	3
Other	1	0
Major bleeding	0	1
Death	0	0
Stroke, death, or major bleeding	3	2

Data given in No.

TIA, transient ischemic attack.

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The power calculation revealed that the sample size for a definitive study would have to be 9752 patients (power set to 0.8 and significance to 0.05). However, Prof Markus mentioned that although it would be very challenging to recruit such a large number of patients, this was a rather wide estimate because of the low number of end points.

In conclusion, Prof Markus highlighted that the recurrent stroke rate in the CADISS trial was much lower than that reported in some observational studies. He also cautioned that the diagnosis of dissection was not confirmed in 20% of cases, suggesting that diagnostic criteria may not always be properly applied in clinical practice.

Endovascular Intervention Beneficial in Pooled Analysis of MR CLEAN and IMS III

Written by Alla Zarifyan

Joseph P. Broderick, MD, University of Cincinnati, Cincinnati, Ohio, USA, reported results of a pooled analysis of patients with a National Institutes of Health Stroke Scale (NIHSS) score ≥ 20 in the MR CLEAN trial [Berkhemer OA et al. *N Engl J Med*. 2015] and IMS III trial [Broderick JP et al. *N Engl J Med*. 2013]. The pooled analysis of the 2 trials examined the efficacy of endovascular therapy in addition to intravenous tissue plasminogen activator (IV tPA) vs IV tPA alone and demonstrated that endovascular therapy after IV tPA improved outcomes in patients presenting with severe stroke.

MR CLEAN was the first study to demonstrate efficacy of intra-arterial treatment received within 6 hours of stroke onset in patients with acute ischemic stroke due to intracranial anterior circulation occlusion. IMS III was terminated due to futility but showed evidence of potential treatment benefit in some patient subgroups, including those with NIHSS ≥ 20. The pooled analysis included all patients in this subgroup from both trials who were treated with IV tPA within 3 hours of onset. However, NIHSS was defined at the time of randomization in MR CLEAN, which was often several hours after starting IV tPA. Thus, an additional exploratory pooled analysis was performed using only those patients from IMS III who had NIHSS ≥ 20 at 40 minutes after starting IV tPA to better approximate MR CLEAN population.

The primary analysis was a logistic ordinal regression on modified Rankin Scale (mRS) at 90 days. The secondary analysis was logistic regression on dichotomized (0-2 vs 3-6) mRS at 90 days.

The pooled analysis included 342 patients (191 in endovascular group vs 151 receiving IV tPA alone). The ordinal analysis of mRS at 90 days favored endovascular intervention with a consistent shift in mRS in both trials and pooled data (adjusted OR, 1.81; 95% CI, 1.21 to 2.70). The dichotomized analysis revealed that 24.1% of patients in the endovascular group had mRS 0 to 2 vs 13.9% receiving IV tPA alone (adjusted OR, 1.85; 95% CI, 1.03 to 3.33).

The exploratory pooled analysis using those patients in IMS III who had NIHSS ≥ 20 at 40 minutes after starting IV tPA included 290 patients (157 in the endovascular group vs 133 receiving IV tPA alone). The following change in NIHSS score occurred in IMS III from pretreatment to 40 minutes: 16 patients worsened to NIHSS ≥ 20, and 68 patients improved to NIHSS < 20.

The ordinal analysis of mRS at 90 days favored endovascular intervention (adjusted OR, 2.07; 95% CI, 1.33 to 3.20). Dr Broderick highlighted that 78% of patients were still not functionally independent even after receiving endovascular therapy in addition to IV tPA. The dichotomized analysis showed that 22.3% of patients had mRS 0 to 2 in the endovascular group vs 10.5% receiving IV tPA alone (adjusted OR, 2.65; 95% CI, 1.31 to 5.34).

Dr Broderick concluded that endovascular therapy after IV tPA improved outcome at 90 days for patients with severe stroke, with no increase in mortality. Also IV tPA treatment was associated with improvement to NIHSS < 20 in approximately a third of patients in the IMS III subgroup of those with NIHSS ≥ 20. He also called for a thoughtful consideration of triage in regional communities for patients with severe stroke who are candidates for endovascular therapy.