Endovascular Treatment for Stroke: The ESCAPE Trial
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Current ischemic stroke management in the ED primarily centers on selective and effective administration of alteplase (also known as tPA) to eliminate intraarterial thrombi. However, a number of studies produced after the initial studies supporting use of tPA in ischemic strokes have demonstrated mixed results. Thus, the medical community has continued to search for better alternatives to treatment of ischemic stroke. One avenue that has been investigated is the use of endovascular clot elimination. A number of studies have been published discussing the benefits (or lack thereof) of endovascular intervention in strokes. One such study was the ESCAPE trial, published in NEJM in February 2015.

Briefly, this study was designed to examine difference between usual care (and the use of tPA, if the patient eligible) and usual care plus endovascular intervention involving retrievable stent usage, if possible. It examined whether patients with ischemic stroke seen on CT/CTA would benefit from endovascular intervention versus the standard of care. The study was initially planned to enroll 500 people, but was stopped after publication of the MR CLEAN trial data, as the authors' data had passed an efficacy threshold set by the authors. MR CLEAN was a trial comparing endovascular treatments with retrievable stenting versus previous generation thrombectomy devices versus the standard of care. The study found improved outcomes in patients treated with endovascular intervention as opposed to the regular standard of care, with or without tPA. The authors of the ESCAPE trial describe the importance of MR CLEAN in the introduction, in addition to mentioning how 60-80% of patients with anterior circulation strokes either die or do not regain functional independence, regardless of tPA use. They describe current hypotheses relating to this outcome; mainly that tPA is ineffective at revascularizing larger vessels with obstructive lesions. Based on this concept, the authors conceived a study utilizing **endovascular treatment for small core and anterior circulation proximal occlusions** with an emphasis on minimizing CT to recanalization times (abbreviated to "ESCAPE"). This study intended to answer the practical question of whether or not a patient should undergo endovascular intervention for ischemic stroke secondary to thrombus.

The study was a prospective, randomized, open-label controlled trial with blinded outcome evaluation at 90 days. Patients were randomized in a 1:1 ratio of intervention:control via an internet program that matched patients based on demographic characteristics. These characteristics included age, sex, NIHSS score, site of arterial occlusion, baseline ASPECTS score, and tPA use. The patients had no upper age limit, were previously independent as determined by a Barthel index score ≥90, and presented at **≤12 hours after symptom onset**. Patients who had noncontrast head CTs and CT angiography needed to have a small infarct core (defined by ASPECTS score of 6-10), a proximal artery occlusion in the anterior circulation (MCA and immediate branches, with or without internal carotid artery involvement), with moderate to good collateral circulation (defined by ≥50% or more of MCA pial arterial circ on CTA). The intervention group underwent a CT angiogram and endovascular intervention with an author recommendation of placement of retrievable stents in appropriate pts, in addition to the standard of care for stroke at their facility (which included alteplase, when indicated). The control groups received the stroke standard of care, which also included alteplase when indicated. The goal times for these patients were a CT to groin puncture of 60 minutes and CT to reperfusion time of 90 minutes. The primary outcome of the study was a change in the modified Rankin Scale at 90 days. Secondary outcomes included early recanalization/reperfusion times,

intracranial hemorrhage, angiography complications, death, and neurologic disability at 90 days. The study was powered to detect a shift in mRS at 90 days after combining scores 5-6 (significant disability and death).

After stopping the study for analysis after publication of the MR CLEAN data, the study had recruited 316 participants from centers in Canada, USA, Republic of Korea, Ireland, and the UK. Researchers randomized 165 patients to the intervention group and 150 patients to the control group (one was excluded due to improper consent procedure). For the primary outcome, researchers found a common odds ratio of 2.6 (95% CI 1.7-3.8) of **improvement of 1 point on mRS after endovascular intervention**. Significant results (all $P<0.05$) showed a median mRS score at 90 days of 2 in the intervention group (compared to 4 in the intervention group), 53% of the intervention group had an mRS of 0-2 (versus 29.3% in the control group), and a 10.4% mortality rate at 90 days (versus 19% in the control group). The interventions were not without risks, however, as they showed an **elevated risk of symptomatic intracranial hemorrhage and device related complications**. Secondary outcomes showed trends toward benefit in the intervention, specifically with higher percentages of Barthel index scores of 95-100 (57.7 vs 36.6) and 90d NIHSS score of 0-2 (51.6 vs 23.1). The study notes no evidence of heterogeneity of effects across groups, but did note that in the 49 patients that received intervention $\geq$6 hours after onset of symptoms, there was only a direction of effect favoring intervention (as opposed to a significant difference seen between intervention and control groups).

One important consideration with regards to the study is the **relationship between the study funding source (Covidien) and the usage of Covidien products**. Of the 165 patients randomized to the intervention, 151 received the intervention. Of the 151 patients, 130 had retrievable stents placed, and 100 of the 130 had Covidien Solitaire stents placed. The study also boasted rapid median time from symptom onset to intervention (241 minutes), time from study CT to reperfusion (84 minutes), and groin puncture to reperfusion of 30 minutes. 113 of 156 patients had a TICI score of 2b or 3 in the intervention group, and 43/138 patients in the control group had an arterial occlusive lesion score of 2 or 3 on follow up CTA.

This study presents a **remarkable break from past studies that have not found any benefit to endovascular intervention in ischemic stroke**. I calculated a number needed to treat to achieve an mRS of 0-2 at 90 days to be 5 patients based on the provided data. However, the number of patients screened for this study was not provided by the researchers, and thus it is unclear how many patients may not be eligible for this type of intervention. Additionally, the short interval times were remarkable, but considering that patients could be excluded from the study if the intervention team was unavailable, one may wonder if patients with longer times may have been excluded. Despite this concern, the trial notes decreased intervention times due to "parallel decision making and action" such as preparing the patient for endovascular intervention before the tPA infusion is complete. The **lack of clear evidence showing benefit for patients in a 6-12 hour post-symptom onset** window is something to be investigated further, especially since intervention options are limited for these patients. Overall, this paper reflects a promising new intervention that can significantly improve morbidity and mortality of patients who experience ischemic stroke.

Reference

Goyal, M., A. M. Demchuk, and B. K. Menon, *et al*. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015; 372: 1019-1030.