Endovascular therapy for acute ischemic stroke is indicated and evidence based: a position statement

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In February 2013, three prospective randomized controlled trials were published simultaneously in the *New England Journal of Medicine*—the Interventional Management of Stroke (IMS III),[1] Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE),[2] and SYNTHESIS-Expansion trials.[3] Each of these studies demonstrated no benefit for endovascular intervention over medical management for patients with acute ischemic stroke (AIS). However, these trials suffered from significant design flaws which were largely related to a very slow rate of patient enrollment, and resulted in the subsequent obsolescence of the imaging protocols and devices used.

Recently, the Multicenter Randomized CLinical trial of Endovascular treatment for AIS in the Netherlands (MR CLEAN), a prospective randomized controlled trial of 500 patients comparing endovascular therapies with medical management for patients with large vessel occlusion (LVO), presented their results at the 9th World Stroke Congress (Istanbul, Turkey 2014).[4] Unlike IMS III and SYNTHESIS-Expansion, LVO was confirmed prior to randomization in all patients. Also, in contrast with MR RESCUE, IMS-III, and SYNTHESIS-Expansion, modern thrombectomy devices were used for the entirety of the trial. Primary and secondary outcomes in MR CLEAN demonstrated a significant benefit for endovascular therapies over medical therapy across all age groups. Furthermore, a second ongoing prospective randomized trial of AIS patients with LVO, Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE), was recently halted by its data safety monitoring board due to the 'overwhelming efficacy' of intra-arterial thrombolysis (IAT) over medical therapy in a preliminary analysis performed in response to the results of MR CLEAN. Similarly, the phase 2 EXTEND-IA trial was halted when a preliminary analysis of the data demonstrated overwhelming efficacy in the interventional cohort. Completion of these three trials has moved the dial forward on the value of mechanical thrombectomy.

A critical and evidence based evaluation of the available data supports the superiority of IAT over standard medical therapies in patients presenting with AIS from LVO within 6 h of stroke onset and having a small infarct core. Moreover, we believe that randomization of these patients in trials, which include a non-interventional arm, may no longer be ethical as general community equipoise appropriately disappears. An examination of the available data is certainly needed to identify those patient populations where equipoise may still exist. In this subset, additional research trials may be informative.

The purpose of this comment is to explain this position based on a rigorous review of the available evidence, historical precedents established in the medical treatment of AIS, and important ethical considerations.

DATA FROM COMPLETED PROSPECTIVE RANDOMIZED TRIALS DEMONSTRATE BENEFIT FROM IAT

One potential argument against the widespread acceptance of IAT superiority is that there have only been two positive trials while there have been three showing no benefit (and one indeterminate). Some would argue that the MR CLEAN results do not outweigh the substantial evidence arguing to the contrary from prior studies. However, there are two robust arguments against this negative interpretation of the existing data.

The majority of the earlier studies had substantial limitations, most notably the lack of LVO confirmation and the use of early generation devices/techniques that had been shown to be inferior to contemporary devices/techniques in prospective randomized trials.[5 6] These limitations were recognized and widely commented on in the published literature.[7 8] Furthermore, subgroup analysis within IMS III itself suggested that confirmation of LVO was a critical step for future trials.[9] Many anticipated that should these design limitations be corrected, subsequent trials would demonstrate the superiority of endovascular treatment. Both of these limitations were addressed in MR CLEAN, wherein LVO was confirmed and 97% of patients underwent recanalization attempts with modern devices. These iterative design changes addressed the limitations of the previous trials, accounting for the subsequent positivity of MR CLEAN.

Even if one considers the available collective evidence for or against IAT produced by these six trials, a meta-analysis published in this journal confirms the beneficial effect of IAT in LVO.[10] The aforementioned statistical analysis was divided into two dataset analyses: (1) an evaluation of IAT versus medical therapy for all patients with pre-randomization LVO confirmation in the completed trials (dataset 1, 1183 total patients); and (2) an evaluation of IAT versus medical therapy for all enrolled patients in all six trials regardless of pre-randomization LVO confirmation (dataset 2, 1903 patients). The prespecified primary endpoint was chosen to be a modified Rankin Scale (mRS) score of 0–2 at 90 days, as this is the most common outcome measure used in modern stroke trials.

The results of this meta-analysis demonstrated superior outcomes with IAT across the six prospective randomized controlled trials (table 1). In patients with pre-randomization LVO confirmation (dataset 1), patients randomized to IAT had 1.67 times greater odds of achieving the primary outcome compared with medical therapy (p=0.0001). If all enrolled patients were analyzed regardless of pre-randomization LVO confirmation, the superiority of IAT remained consistent (OR 1.27, p=0.018). Although this meta-analysis is limited by

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Table 1 Meta-analysis primary and secondary outcome analyses for the two datasets using a weighted fixed effect model Fargen *et al*[10]

Outcome measure	IA arm (n (%) unweighted)	Medical arm (n (%) unweighted)	OR (95% CI), p value
Included studies with LVO confirmed at time of randomization (dataset 1)			
Primary outcome			
mRS 0–2 at 90 days	251 (38.3)	136 (25.8)	1.67 (1.29 to 2.16), p=0.0001
Secondary outcomes			
mRS 0–1 at 90 days	156 (23.8)	66 (12.5)	1.93 (1.39 to 2.68), p<0.0001
mRS 0–3 at 90 days	348 (53.1)	224 (42.4)	1.46 (1.16 to 1.85), p=0.002
Mortality at 90 days	122 (18.6)	114 (21.6)	0.80 (0.60 to 1.07), p=0.13
mRS shift analysis (mean)	3.35	3.73	p<0.0001
All included studies (dataset 2)			
Primary outcome			
mRS 0–2 at 90 days	419 (39.1)	271 (32.6)	1.27 (1.04 to 1.54), p=0.018
Secondary outcomes			
mRS 0–1 at 90 days	270 (25.2)	169 (20.3)	1.22 (0.97 to 1.53), p=0.09
mRS 0–3 at 90 days	600 (56.0)	412 (49.5)	1.25 (1.04 to 1.51), p=0.019
Mortality at 90 days	203 (19.0)	156 (18.8)	0.96 (0.76 to 1.22), p=0.73
mRS shift analysis (mean)	3.16	3.42	p=0.003

IA, intra-arterial; LVO, large vessel occlusion; mRS, modified Rankin score.

the inherent heterogeneity of the six included trials, it provides strong evidence in support of IAT over medical therapy for AIS patients presenting with LVO.

INTRAVENOUS TISSUE PLASMINOGEN ACTIVATOR AS AN HISTORICAL PRECEDENT SUGGESTS THERE IS ENOUGH DATA TO SUPPORT IAT

The use of intravenous tissue plasminogen activator (IV tPA) is a well accepted standard of care treatment for patients presenting with AIS within the first 4.5 h after symptom onset, and is endorsed by the American Heart Association/American Stroke Association and the American Academy of Neurology. However, if we examine the evidence through which IV t-PA became a mainstay and routine therapy for stroke patients, an important corollary to IAT becomes evident. Consider the representative evidence from the 12 major randomized trials evaluating the benefit of IV thrombolysis compared with standard medical care (table 2).

The landmark trial through which IV thrombolysis gained widespread acceptance as a standard of care therapy for stroke is the National Institute of Neurological Disorders and Stroke (NINDS) recombinant tPA Stroke Study Group trial, published in 1995.[11] Interestingly, in part 1 of this trial (291 patients), no benefit of IV tPA was identified. Only in part 2 (333 patients) was IV tPA beneficial in improving outcomes, and this was only with a global statistic and with a requirement that half of the patients be enrolled within 90 min. Despite these significant limitations, IV tPA was accepted as a standard for all patients presenting within 3 h of symptom onset. Further, in an effort to extend IV tPA beyond 3 h, the first and second European Cooperative Acute Stroke Study (ECASS) trials,[12 13] accounting for over 1400 patients treated between 3 and 6 h, demonstrated no benefit of IV thrombolysis beyond the 3 h window. Indeed, the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) trial, containing 613 patients, of a planned enrollment of more than 900, treated from 3 to 5 h with IV tPA, was halted for futility.[14] Despite the negative data from these multiple major trials containing over 2000 enrolled patients, the stroke community accepted

Table 2 Review of 12 major intravenous thrombolysis randomized trials

Study	Agent	Time (h)	IV treatment (n)	Placebo treatment (n)	Primary outcome	Result
NINDS, 1995 (Part 2)[11]	tPA	0–3	168	165	Favorable outcome*†	Positive (OR 1.7, 95% CI 1.2 to 2.6)
ECASS, 1995[12]	tPA	0–6	313	307	Improvement in Barthel Index by 15 at 90 days	No benefit (p=0.99)
MAST-1, 1995[16]	Streptokinase	0–6	157 streptokinase alone, 156 streptokinase+ASA	153 ASA alone, 156 placebo	6 month case fatality or disability	No benefit (OR 0.9, 95% CI 0.7 to 1.3)
MAST-E, 1996[17]	Streptokinase	0–6	156	154	mRS ≥3 at 6 months	No benefit (p=0.60)
ASK Trial, 1996[18]	Streptokinase	0–4	174 (41<3 h, 133>3 h)	166 (29<3 h, 137>3 h)	Alive with Barthel score ≥60	No benefit (OR 1.08, 95% CI 0.74 to 1.86)
ECASS II, 1998[13]	tPA	0–6	409	391	mRS 0 or 1 at 90 days	No benefit (0.28)
ATLANTIS, 1999[14]	tPA	3–5	272	275	NIHSS 0 or 1 at 90 days	No benefit (p=0.65)
A0276g, 2000[19]	tPA	0–6	71	71	>3 NIHSS improvement or complete recovery at 30 days	No benefit (p=0.05, in favor of placebo)
EPITHET, 2008[20]	tPA	3–6	52	49	Infarct growth†	No benefit (p=0.24)
ECASS III, 2008[15]	tPA	3–4.5	418	403	mRS of 0 or 1 at 90 days	Positive (OR 1.34, p=0.04)
DIAS-2[21], 2009	Desmoteplase	3–9	57 low dose, 66 high dose	63	Clinical response rate*	No benefit (p=0.47)
IST-3, 2012[22]	tPA	0–6	1515	1520	Oxford handicap score of 0–2 at 6 months	No benefit (p=0.18)

*Composite of improvement in NIHSS of 8 points or more or an NIHSS score of 1 point or less, an mRS of 0–2, and a Barthel Index of 75–100.
†Between admission diffusion weighted imaging and day 90 T2 lesion.
ASA, acetylsalicylic acid; IV, intravenous; mRS, modified Rankin score; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator.

IV tPA as a standard of care therapy and expanded the time window to 4.5 hr after the third ECASS trial was published in 2008 (containing 821 patients), demonstrating superior outcomes for patients treated within the 3–4.5 h time period.[15]

The historical precedent established by these IV tPA trials suggests that, based on the available evidence for IAT after the presentation of the results of MR CLEAN, enough data are present to accept the superiority of IAT over medical therapy for at least a significant portion of patients presenting within 0–6 h with a confirmed LVO.

AN ETHICAL OBLIGATION EXISTS TO OFFER IAT

The goal of a randomized controlled trial is to compare two or more treatments thought to be equivalent (clinical equipoise), to provide the best available evidence for one treatment or another, and to establish practice patterns that lead to the best patient outcomes. In the setting of AIS secondary to LVO, the clinical equipoise required to continue the ethical randomization of patients in controlled trials demands that the two treatment options (medical therapy and IAT) remain equivalent based on the best available evidence. Once superiority has been established, it is unethical to continue randomizing patients to a treatment that is known to be inferior. To continue to do so is to condemn patients to worse outcomes. Clinical equipoise, therefore, is essential for the ethical treatment of patients as it pertains to trials.

The presented results of MR CLEAN demonstrating the superiority of IAT and the early cessation of ESCAPE and EXTEND IA due to overwhelming superiority of IAT, as well as the meta-analysis of the six completed prospective randomized controlled trials, all support the lack of clinical equipoise. Certainly, as the data from MR CLEAN, ESCAPE, EXTEND IA, and other recently halted trials become available, there will be cohorts in whom equipoise still exists and further randomized trials are indicated. Trials might also be appropriately undertaken to answer questions regarding optimization of patient selection, treatment options, and systems of care. This is the very nature of progress in scientific inquiry.

CONCLUSIONS

The overwhelmingly positive results of MR CLEAN, when considered along with the other five randomized controlled trials evaluating IAT, affirm the superiority of IAT over standard medical care for patients with LVO presenting within 0–6 h.

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