Endovascular treatment for acute ischemic stroke patients: implications and interpretation of IMS III, MR RESCUE, and SYNTHESIS EXPANSION trials: a report from the Working Group of International Congress of Interventional Neurology

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Abstract

Objective: The results of Interventional Management of Stroke (IMS) III, Magnetic Resonance and REcanalization of Stroke Clots Using Embolectomy (MR RESCUE), and SYNTHESIS EXPANSION trials are expected to affect the practice of endovascular treatment for acute ischemic stroke. The purpose of this report is to review the components of the designs and methods of these trials and to describe the influence of those components on the interpretation of trial results.

Methods: A critical review of trial design and conduct of IMS III, MR RESCUE, and SYNTHESIS EXPANSION is performed with emphasis on patient selection, shortcomings in procedural aspects, and methodology of data ascertainment and analysis. The influence of each component is estimated based on published literature including multicenter clinical trials reporting on endovascular treatment for acute ischemic stroke and myocardial infarction.

Results: We critically examined the time interval between symptom onset and treatment and rates of angiographic recanalization to differentiate between "endovascular treatment" and "parameter optimized endovascular treatment" as it relates to the IMS III, MR RESCUE, and SYNTHESIS EXPANSION trials. All the three trials failed to effectively test "parameter optimized endovascular treatment" due to the delay between symptom onset and treatment and less than optimal rates of recanalization. In all the three trials, the magnitude of benefit with endovascular treatment required to reject the null hypothesis was larger than could be expected based on previous studies. The IMS III and SYNTHESIS EXPANSION trials demonstrated that rates of symptomatic intracerebral hemorrhages subsequent to treatment are similar between IV thrombolytics and endovascular treatment in matched acute ischemic stroke patients. The trials also indirectly validated the superiority/equivalence of IV thrombolytics (compared with endovascular treatment) in patients with minor neurological deficits and those without large vessel occlusion on computed tomographic/magnetic resonance angiography.

Conclusions: The results do not support a large magnitude benefit of endovascular treatment in subjects randomized in all the three trials. The possibility that benefits of a smaller magnitude exist in certain patient populations cannot be excluded. Large magnitude benefits can be expected with implementation of "parameter optimized endovascular treatment" in patients with ischemic stroke who are candidates for IV thrombolytics.

Keywords

Published May, 2014.

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Table 1. Summary of results of IMS III, MR-RESCUE, and SYNTHESIS EXPANSION trials

	IMS III		MR RESCUE		SYNTHESIS EXPANSION	
	Endovascular treatment	IV alteplase only	Endovascular treatment	Standard treatment	Endovascular treatment	IV alteplase only
N	434	222	64	54	181	181
Mean age (±SD)	69 (23–89) [*] *	68 (23–84) [*] *	64 ± 17.8	67.6 ± 23	66 ± 11	67 ± 11
Median NIHSS score (range)	17 (7–40)	16 (8–30)	17.5 (12–22)	18 (11–23)	13 (2–26)	13 (9–18)
IV alteplase	100%	100%	44%	30%	Not used	98%
TICI 2-3[†]†	75%	NR	67%	NR	NR	NR
TICI 2B-3	41%	NR	27%	NR	NR	NR
mRS 0–1	29.4%	27.1%	23%	33%	30.4%	34.8%
mRS 0–2	42.7%	40.2%	37.5	61%	42%	46.4%
Symptomatic ICH	6.2%	5.9%	4.7	3.7	6%	6%
Any ICH	27.4%	18.9%	66%	48%	NR	NR

Note:*NIHSS* National Institutes of Health Stroke Scale; **NR**: not reported; *TICI* thrombolysis in cerebral infarction; *mRS* modified Rankin scale; *ICH* intracerebral hemorrhage

[†]**0** No perfusion;

1 Perfusion past the initial obstruction but limited distal branch filling with little or slow distal perfusion;

2a Perfusion of less than 1/2 of the vascular distribution of the occluded artery; less than 2/3 for MR-RESCUE;

2b Perfusion of 1/2 or greater of the vascular distribution of the occluded artery; 2/3 or greater for MR-RESCUE; and

3 Full perfusion with filling of all distal branches.

[*] Median (range).

Introduction

Endovascular treatment of acute ischemic stroke represents several therapeutic interventions including both drugs and devices introduced through catheters or microcatheters placed in the intracranial arteries using a percutaneous approach [1]. Several thrombolytic medications have been used in various doses and concentrations as part of the endovascular treatment. These include urokinase, alteplase, reteplase, and tenecteplase [2]. The devices are categorized into thrombectomy with thrombus retrieval (coil platform, aspiration platform, and stent platform) or without retrieval (angioplasty balloon catheters, and stents). Proximal flow arrest by balloon inflation in the carotid or vertebral arteries may be used to prevent forward movement of a thrombus or thrombus fragments [3,4]. Intravenous (IV) heparin during the procedure in the form of a bolus or infusion has been used in various protocols [5]. Further, IV platelet glycoprotein IIB/IIIA inhibitors have been infrequently used during and after the procedure [6].

Three recent trials have evaluated the therapeutic efficacy of endovascular treatment in patients with acute ischemic stroke. The purpose of this report is to review the design and results of these trials and determine implications of these trials on current practices by objectively interpreting the findings.

Summary of trials

The Interventional Management of Stroke (IMS) III trial randomly assigned eligible patients who had received IV alteplase (recombinant tissue plasminogen activator (rt = PA), alteplase) within 3 h after symptom onset to receive additional endovascular treatment or no additional treatment, in a 2:1 ratio [7]. The angiographic procedure had to begin within 5 h and be completed within 7 h after the onset of stroke. The primary outcome measure was a modified Rankin scale (mRS) score of 2 or less at 90 days (see Table 1). The trial was discontinued after 656 participants had undergone randomization (434 patients to endovascular therapy and 222 to IV alteplase) because of futility. The proportion of participants with the desired primary outcome at 90 days was not statistically significant among patients treated with endovascular treatment and those treated with IV alteplase (predominantly absolute adjusted difference, 1.5 %; 95% confidence interval [CI], –6.1 to 9.1). The proportion of patients with symptomatic intracerebral hemorrhage (ICH) within 30 h after initiation of IV alteplase was similar between the two groups (6.2% and 5.9%, *P=* 0.8). Predefined secondary analysis showed no signifi-

cant difference between the groups although there was a trend towards better outcome in the endovascular group in those treated within 2 h and those with time from IV tPA to groin puncture of less than 90 min.

The SYNTHESIS EXPANSION [8] trial randomly assigned 362 patients with acute ischemic stroke, within 4.5 h after onset, to endovascular treatment, which was predominantly intra-arterial [IA] thrombolysis and the option of mechanical thrombectomy left to the discretion of the treating physician, or IV alteplase [8]. In patients with a neurologic deficit but no corresponding occlusion, the endovascular procedure involved injecting rt-PA into the vascular area that was presumed to be affected. A total of 181 patients were randomized to receive endovascular therapy, and 181 to receive IV alteplase. The primary outcome was defined by a mRS of 0 or 1 at 3 months. The primary outcome was seen in 30.4% of the patients treated with endovascular-treatment and 34.8% of those treated with IV alteplase at 3 months. After adjustment for age, sex, stroke severity, and atrial fibrillation status at baseline, the odds of primary outcome was not statistically significant (odds ratio [OR] adjusted, 0.71; 95% confidence interval [CI], 0.44 to 1.14; $P= 0.16$). Symptomatic ICH within 7 days occurred in 6% of the patients in each group. There was a trend towards better outcome in the IV group in patients older than 67 years and those with the National Institutes of Health Stroke Scale (NIHSS) score of <11.

The (Magnetic Resonance and REcanalization of Stroke Clots Using Embolectomy) MR RESCUE trial [9] randomly assigned ischemic stroke patients with large-vessel, anterior-circulation occlusion within 8 h after symptom onset to either mechanical embolectomy (Merci retriever or penumbra system) with optional IA alteplase at a dose up to 14 mg or standard care, including IV alteplase for eligible patients [9]. Patients were stratified by the presence of a favorable penumbral pattern (substantial salvageable tissue and small infarct core) or not, prior to randomization on pretreatment computed tomography (CT) or magnetic resonance imaging (MRI) of the brain. A total of 118 patients were included in the primary analysis (58% had a favorable penumbral pattern). Sixty-four patients were assigned to undergo embolectomy, of which 34 had a favorable penumbral pattern and 54 patients were assigned to receive standard care, of which 34 had a favorable penumbral pattern. The mean scores on the mRS at 3 months did not differ between embolectomy and standard care (3.9 vs. 3.9, $P= 0.99$). Symptomatic ICH was seen in 3 and 2 of the 64 and 54 patients randomized to embolectomy or standard care. Patients with penumbral pattern had smaller infarct

volumes and lower mRS at 90 days regardless of the treatment modality.

Evolution of endovascular treatment

Historical perspective

Randomized trials [10,11] have demonstrated the benefit of using IV alteplase for patients with ischemic stroke presenting within 3 h and 3 to 4.5 h (in selected patients) of symptom onset. However, endovascular treatment was promoted because 57–58% of the patients who received IV alteplase still had death or disability as a consequence of the ischemic stroke [10,12]. Prolyse in Acute Cerebral Thromboembolism II (PROACT II), was a randomized, controlled, multicenter trial that was conducted prior to widespread acceptance of IV alteplase [13]. A total of 180 patients with acute ischemic stroke and symptom onset < 6 h with angiographically confirmed occlusion of the middle cerebral artery (MCA) were randomized to receive 9 mg of IA recombinant pro-urokinase (r-proUK) plus heparin (n = 121) or heparin only (n = 59). The recanalization rate was 66% and 18% for the r-proUK group and control group after 2 h of r-proUK or placebo infusion, respectively. At 90 days post-randomization, 40% of r-proUK patients and 25% of control patients had a mRS score 0–2 ($P = 0.04$). Symptomatic ICH within 24 h occurred in 10% of r-proUK patients and 2% of control patients. While a direct comparison between IV alteplase and IA r-proUK was not available, the benefit seen in patients treated with IA r-proUK was considered the basis for endovascular treatment in patients presenting after 3 h.

Subsequent trials were single arm non-randomized trials evaluating coil based or aspiration based thrombectomy devices using historical controls derived from the PROACT II placebo group [14]. The Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial demonstrated that recanalization rates were higher with embolectomy device (Merci Retriever, Concentric Medical, Mountain View, California) compared with historical controls derived from PROACT II placebo group (46% vs. 18%), and recanalization was associated with higher rates of mRS score 0–2 at 90 days in the treated cohort. The Merci Retriever was granted approval through the 510(k) process because the Merci Retriever was felt to be substantially equivalent to a predicate device [15]. The predicate device was the Concentric Retriever, which received 510(k) clearance by the Food and Drug Administration (FDA) in May 2001 for "use in the retrieval of foreign bodies in the peripheral, coronary, and neuro vasculature." In August, 2004 the FDA gave approval for the first medical device specifically indica-

ted to retrieve blood clots from the brain in ischemic stroke for patients who fail or are ineligible for IV alteplase [16]. Subsequently, a prospective, multicenter, single-arm study reported that upon 125 patients who were treated by the Penumbra (aspiration) System (Penumbra, Alameda, California) [17]. partial or complete recanalization was seen in 82% of the treated arteries which was higher than the pre-specified threshold of ≥60% used to define adequate effectiveness in recanalization. Recanalization was associated with higher rates of mRS score 0–2 at 90 days. Further, FDA approval in January 2008 occurred after the Penumbra device was judged to be "substantially equivalent" to the Merci retriever for revascularization of patients with acute ischemic stroke secondary to large vessel occlusive disease within 8 h of symptom onset.

Various criteria were proposed or used for selection of patients to undergo endovascular intervention included presentation between 3 h and 8 h after symptom onset, severe neurological deficits (NIHSS score ≥10), recent history of major surgical procedures (within 14 days), and occlusion of major cervical or intracranial vessels. A major milestone in expansion of endovascular treatment was the recognition that endovascular treatment can be safely administered after receiving IV alteplase [18].

Assessment of utilization

One study evaluated the trends in utilization of endovascular treatment and associated rates of death and disability among acute ischemic stroke patients over a 6-year period (2004–2009) [19]. Of the 3,292,842 patients admitted with ischemic stroke, 72,342 (2.2%) received IV thrombolytic treatment and 13,799 (0.4%) underwent endovascular treatment. There was a sixfold increase in patients who underwent endovascular treatment (0.1% of ischemic strokes in 2004 vs. 0.6% in 2009; $P < 0.001$). While the mortality associated with endovascular treatment decreased, the moderate-to-severe disability increased without a change in none to minimal disability rates. In a population-based study [20], the incidence of endovascular thrombectomy for acute ischemic stroke varied based on patients' age ranging from 22.8 per 100,000 person in population aged 75–84 years to 18.1 per 100,000 persons in population aged ≥85 years in 2008 and 2009; in contrast, the incidence of IV thrombolysis increased from 91.2 per 100,000 persons in population aged 75–84 years to 130.9 per 100,000 persons in population aged ≥85 years.

IA versus IV thrombolytic treatment

Despite the theoretical assumption that IA administration of thrombolytics can achieve a much higher concen-

tration of thrombolytic within the thrombus, clinical studies have not unequivocally confirmed the superiority of IA over IV thrombolytics. Our understanding of comparative efficacy between IV and IA thrombolytic administration is derived from studies performed in experimental models and patients with acute myocardial infarction (MI) and ischemic stroke. The data are summarized hereunder.

Comparative data from experimental and clinical acute MI studies

Compared with IV administration, the rate and extent of coronary thrombolysis were increased with intracoronary administration in experimental models of coronary thrombosis [21,22] and small clinical studies [23,24]. However, in one porcine model, IA and IV administration of urokinase resulted in the same rate of thrombus resolution [25]. A pooled analysis of nine studies comparing IV streptokinase and intracoronary streptokinase in the treatment of acute MI determined a similar success rate of recanalization: 73% for IV streptokinase and 72% for intracoronary streptokinase [26]. In another subsequent angiographic study, anisoylated plasminogen streptokinase activator complex administered IV and intracoronary streptokinase achieved the same rate of reperfusion in patients with acute MI [27]. The efficacy of IV thrombolysis was almost equivalent to intracoronary thrombolysis within the first 3 to 4 h after symptom onset but may be lower in later time frames for unclear reasons [28,29]. In a multicenter trial [30] in patients with acute MI, recanalization rates were higher with IA compared to IV thrombolytics (60% vs. 51%). The difference was most pronounced in patients treated after 4 h of symptom onset because the rate of recanalization decreased from 60% to 33% with IV thrombolysis.

Comparative data from experimental models of acute ischemic stroke

In experimental models of cerebral artery thrombosis, no clear superiority of IA thrombolytic administration could be demonstrated in comparison with IV administration. In one study using a rat model of embolic ischemic stroke, 2-h infusion with IA r-proUK, IV r-proUK, or placebo was administered after 30 min of ischemia onset [31]. Both IA and IV r-proUK improved the percentage of the ischemic hemisphere with normal perfusion compared with placebo with no difference between the two routes of r-proUK. Another study compared the rates of recanalization, cerebral infarct, and hemorrhage between IA reteplase and IV alteplase in a canine model of basilar artery thrombosis [32]. Two hours after thrombosis, the canines were randomized in a blinded fashion

to receive IV alteplase (0.9 mg/kg over 60 min) and IA placebo, or IA reteplase 0.09 units/kg over 20 min, equivalent to one-half the alteplase dose, and IV placebo. At 6 h, no significant difference in partial or complete recanalization was observed. Postmortem MRI revealed infarcts in four of six animals treated with IV alteplase and three of seven treated with IA reteplase ($P = 0.4$).

Comparative data from clinical acute ischemic stroke studies

No previous randomized trial has demonstrated the superiority of IA thrombolytics over IV thrombolytics in acute ischemic stroke patients.

IV alteplase and endovascular treatment combination

The idea that the effect of combining IV and IA thrombolysis is greater than the sum of their separate effect stems from the hypothesis of higher vulnerability of a thrombus that is already primed by the circulating IV alteplase to additional mechanical and/or pharmacological thrombolysis. However, studies have shown that in acute MI patients, intracoronary streptokinase results in none or small rates of additional reperfusion after failure to recanalize with IV streptokinase [33,34]. Among ischemic stroke patients, the data supported additional recanalization with endovascular treatment in patients who had received IV alteplase but the benefit in reducing death and disability remains unproven. Emergency Management of Stroke (EMS) Bridging trial, [35] randomly assigned 35 patients to received IV alteplase or IV placebo prior to receiving IA alteplase. Recanalization was better ($P= 0.03$) in the IV alteplase prior to receiving IA alteplase group with complete recanalization seen in 6 of 11 patients versus 1 of 10 in placebo followed by IA treated patients ($P=0.05$). The recanalization as measured by Thrombolysis In Myocardial Infarction (TIMI) score [36] correlated to the total dose of alteplase given (correlation coefficient 0.36, $P= 0.05$). The mean alteplase dose administered was 20 mg for no recanalization and 57 mg for those with complete recanalization.

A single center study of 25 patients treated with IV followed by IA thrombolytics were compared to 25 patients treated with IA thrombolytics alone after propensity matching [37]. There was a significant difference in time to treatment (mean of 151 min for the combined group and 261 min for the IA alone, $P < 0.001$) and IA alteplase dose (17.5 mg for IV/IA vs 22.8 mg for IA only, $P = 0.05$). However, total dose administered was higher in those treated with IV followed by IA thrombolytics alteplase. Recanalization was 64% with IV followed by IA thrombolytics versus 48% with IA thrombolytics alone. The rate of mRS 0–2 was non-significantly higher in those who received IV/IA alteplase. In a post-hoc analysis of MultiMERCI trial, a comparison was made between patients who received IV alteplase but did not demonstrate any clinical improvement and those who were ineligible for IV alteplase [38]. Both groups were treated with mechanical thrombectomy with or without IA alteplase. There was no difference in revascularization rate, mortality rate, symptomatic ICH rate, or the rate of good functional outcome (mRS 0–2) at 90 days. Another study compared results of endovascular treatment with use of stents with no endovascular treatment in patients with MCA occlusion who either failed to respond to IV alteplase or have contraindications to IV alteplase [39]. The rate of mRS 0–2 was significantly higher in those treated with follow-up endovascular treatment [43.5% vs. 15.4%].

Critique of patient selection in the IMS III, MR RESCUE, and SYNTHESIS EXPANSION trials

Inclusion of patients with minor ischemic deficits

Inclusion of patients with low NIHSS scores can predispose overall patient population to have a high rate of favorable outcome (discussed hereunder) regardless of treatment (ceiling effect) making it difficult to discern the beneficial effect of endovascular treatment. Minimal or no disability (mRS 0 to 1) was seen in 33 of 42 (79%) subjects with minor ischemic symptoms (NIHSS score <6) treated with IV alteplase and 13 of 16 (81%) subjects treated with placebo in the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA trial [40]. In another study, 96 of 136 patients (71%) with initial NIHSS score of <6 had a mRS 0 to 1 at 90 days without any thrombolytic treatment [41]. In the SYNTHESIS EXPANSION trial, [8] no pre-specified NIHSS score threshold or pre-procedure demonstration of large arterial occlusion was required. The NIHSS scores ranged from 2 to 26 in patients who underwent endovascular treatment. Inclusion of a large proportion of the 129 of 362 patients (36%) with NIHSS score of <11 in SYNTHESIS EXPANSION [8] may have reduced the ability to detect incremental benefit of endovascular treatment. Among the 129 patients with NIHSS score of <11, the rate of favorable outcome was prominently higher among IV alteplase treated patients (59% vs.

49%, *P* = 0.14). The IMS III [7] trial and MR RESCUE [9] trial included patients with baseline NIHSS score of ≥10 (8 to 9 with documented arterial occlusion) and from 6 to 29, respectively. The IMS III [7] trial found a non-significant trend towards benefit of endovascular treatment among patients with NIHSS score of ≥20 (n=204; *P* = 0.06). This trend was not observed in patients with NIHSS score of 8 to 19, (n=452; *P* = 0.83). Overall, these trials demonstrate that the benefit of endovascular treatment may be seen in patients with major ischemic deficits and not in those with minor ischemic stroke.

Lack of confirmation of arterial occlusion prior to endovascular treatment

In both the IMS III [7] and SYNTHESIS EXPANSION trials, confirmation of arterial occlusion by CT or MR angiography prior to endovascular treatment was not required. Demonstration of large arterial occlusion using CT or MR angiography was required for patients with NIHSS score of 8 to 9 in IMS III [7] trial and for those treated with IV alteplase in MR RESCUE [9] trial. In the IMS III [7] trial, 89 of 423 patients randomized to endovascular treatment did not receive any endovascular treatment. In 80 of the 89 patients that did not receive endovascular treatment, lack of thrombus deemed treatable by endovascular therapy by site investigator was the primary reason. Of the 181 patients assigned to endovascular treatment in SYNTHESIS EXPANSION trial, [8] IA alteplase (0.9 mg/kg) was administered in the absence of arterial occlusion. Overall, 15 patients did not receive the treatment (6 because of clinical improvement, 3 because of a lack of evidence of occlusion, 3 because of dissection, and other reasons in 3 patients). In the MR RESCUE, [9] 5 of 70 patients randomized to embolectomy were not treated due to lack of arterial occlusion on vessel imaging. Consistent documentation of arterial occlusion prior to randomization may have identified a patient group more likely to benefit from endovascular treatment. In a cohort of patients with CT scan demonstrated hyperdense MCA, a surrogate for large artery occlusion, IA thrombolysis was associated with higher rates of mRS 0-2 at 3 months compared with IV thrombolysis (53% versus 23%)[134]. Furthermore, a large proportion of patients who were not treated but are considered in the endovascular treatment group based on intent-to-treat analysis obscure the effectiveness estimates of endovascular treatment.

Low enrollment rate of patients with basilar artery distribution ischemic stroke

In the IMS III trial [7], the presumptive location of the stroke was in the brainstem or cerebellum in 14 of 656

patients included in analysis. Only 4 patients had basilar artery occlusions in the 434 patients randomized to endovascular treatment. In the SYNTHESIS EXPANSION trial, [8] 29 of the 362 patients had ischemic stroke referable to the posterior circulation. However, MR RESCUE [9] trial did not include patients with posterior circulation ischemic stroke in the trial. Therefore, all the three trials are not a representation of comparative effectiveness of endovascular treatment and either IV alteplase or standard treatment in patients with basilar artery occlusion or posterior circulation ischemic stroke. The rate of death and disability remains high in patients with basilar artery occlusion treated with IV alteplase [42,43].

Endovascular treatment has been preferentially considered in patients with acute basilar artery occlusion due to the high rates of death and disability seen following IV alteplase treatment. In a randomized controlled trial, IA urokinase within 24 h of symptom onset in patients with angiographic evidence of posterior circulation vascular occlusion resulted in higher rates of good outcomes (4 of 8) compared with 1 of 8 patients in the control group [44]. The Basilar Artery International Cooperation Study [45] (BASICS) did not support unequivocal superiority of IA thrombolysis over IV alteplase but recommended a randomized clinical trial to further evaluate the comparative effectiveness of both treatments.

Low enrollment rate of patients with atrial fibrillation related ischemic stroke in SYNTHESIS EXPANSION trial

Underlying atrial fibrillation was seen in 12% of the patients randomized in the SYNTHESIS EXPANSION [8] trial which was almost one-third of the proportion of patients with atrial fibrillation randomized in IMS III [7] and MR RESCUE trials [9]. In the IMS III trial, atrial fibrillation was present in 34% of the subjects included in the final analysis. Presence of atrial fibrillation was associated with lack of early recanalization in patients following IV alteplase treatment (74% vs. 38%) in one study [46]. A subsequent study reported higher rates of worsening at 7 days and poor outcome (mRS >3 and death) at 3 months after IV alteplase in patients with atrial fibrillation compared with those without atrial fibrillation [47]. The results of endovascular treatment do not demonstrate any significant differences in the outcomes between patients with and without atrial fibrillation suggesting a preferential role in this patient population [48,49]. A higher proportion of patients with atrial fibrillation in the SYNTHESIS EXPANSION trial [8] may have resulted in greater ability to detect a benefit of endovascular treatment compared with IV alteplase. It
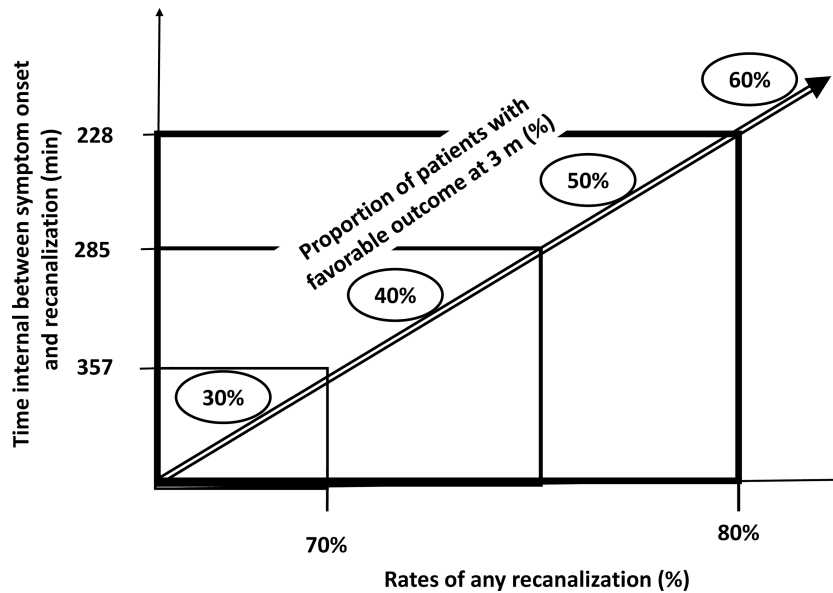
Figure 1. The relationship of time interval between symptom onset and treatment, and post-procedure recanalization with favorable outcome (mRS 0–2 at 1–3 months).

should be noted that in a non-randomized comparison, the patients who received IV alteplase had higher rates of favorable outcome compared with controls that was not diminished in the presence of atrial fibrillation [50].

Inadequate rates of parameter optimized endovascular treatment in IMS III, SYNTHESIS EXPANSION, and MR RESCUE trials

Performance of endovascular procedure alone cannot be fully effective in acute ischemic stroke settings without achieving "timely reperfusion" to the ischemic region of the brain. There are four main reasons for lack of benefit following endovascular treatment: (1) Lack of recanalization; (2) Recanalization without matching reperfusion (microvascular compromise); (3) Reperfusion into irreversibly damaged ischemic region or (4) Procedure-related complications. The latter three phenomena result in "futile recanalization" following endovascular treatment [51]. We critically examine these factors in subsequent sections to differentiate between "endovascular treatment" and "effective endovascular treatment" as it relates to the IMS III, [7] MR RESCUE, [9] and SYN-THESIS EXPANSION trials [8].

"Parameter optimized endovascular treatment" is an endovascular treatment that achieves high rates of recanalization without a high rate of futile recanalization. The

goal of parameter optimized endovascular treatment is to provide rates of favorable outcome defined by mRS 0 to 2 at 3 months of 50% or greater in a patient population with expected favorable outcome of less than 40% with IV alteplase alone at 3 months. The thresholds for defining acceptable rates of recanalization and time interval between symptom onset and treatment to achieve the above mentioned goals are not completely defined. Figure 1 was derived from two studies to demonstrate the relationship between time interval between symptom onset and endovascular treatment, rate of recanalization, and rate of favorable outcome (mRS 0 to 2). The relationship between time interval and outcome was based on a collaborative pooled analysis of 7 endovascular databases including a total of 480 patients [52]. The relationship of rates of recanalization with rates of favorable outcomes was assessed by an analysis of 15 studies including 559 patients [53]. A combined interpretation of both studies would suggest that achieving treatment time of <225 min and resulting in ≥80% rate of recanalization would result in 50% or greater rate of favorable outcomes (mRS 0 to 2) and this concept form the quantitative basis of "parameters optimized endovascular treatment" (see Figure 1).

Critical analysis of time interval between symptom onset and endovascular treatment in IMS III, SYNTHESIS EXPANSION, and MR RESCUE trials

The time interval between symptom onset and recanalization is the most important time interval from a physiological standpoint. The results from single-group IMS I and II trials and the RECANALISE study indicate that the link between recanalization and outcome is rapidly attenuated with increasing time from the onset of symptoms to reperfusion [54,55]. In the IMS I and II trials, a 30-min delay was associated with a 10% decrease in the probability of functional independence (defined as a mRS of 0, 1, or 2) [54,55]. Recanalization was not associated with improved outcome compared with cases without angiographic reperfusion at 350 min.

In the IMS III trial, [7] the time interval between IV alteplase administration and initiation of endovascular treatment was ≤90 min in 242 patients and >90 min in 177 patients. The mean time interval between symptom onset and endovascular treatment was: mean (SD) 249.4 (50.6) mins, which was about 32 min longer than in the IMS I trial [56]. In the SYNTHESIS EXPANSION trial, patients in the endovascular arm were treated an hour later than those in the IV arm, with median time between symptom onset and treatment of 3.75 h (225 min) and 2.75 h of endovascular and IV alteplase, respectively. In the MR RESCUE trial, [9] mean time from symptom onset to initiation of procedure (groin puncture) was 6 h 21 min (SD 1 h 14 min). Mean time from CT scan to femoral puncture was 2 h 4 min (SD 56 min).

While the exact proportion of patients who met the threshold for time interval between symptom onset and treatment in these trials is not known, approximately half of the subjects recruited in IMS III [7] and SYNTHESIS EXPANSION [8] trials and none of the subjects recruited in MR RESCUE [9] met these threshold values. Therefore, it is possible that the rates of favorable outcome at 90 days in the IMSIII [7] and SYNTHESIS EXPANSION [8] trials would have been higher if a larger proportion of patients had received endovascular treatment at an earlier time interval. An analysis of the IMS III trial [7] confirmed the possibility of greater benefit with earlier time to treatment within the study cohort. There was a trend towards loss of clinical benefit in patients treated with endovascular treatment if the time interval between IV alteplase initiation and femoral puncture was >90 min.

Rates of recanalization in IMS III, SYNTHESIS EXPANSION, and MR RESCUE trials

Angiographic recanalization was assessed with post-procedure angiography using Thrombolysis in Cerebral Infarction (TICI) scale, which ranges from 0 (no perfusion) to 3 (full perfusion) in IMS III [7] and MR RESCUE [9]. Partial or complete revascularization was defined as a TICI score of 2a to 3. In general, the rates of recanalization following endovascular treatment did not meet the thresholds required for "parameter optimized endovascular treatment" in IMS III [7] and MR RESCUE [9] trials (not reported in SYNTHESIS EXPANSION trial [8]). In IMS III [7] patients, the rate of partial or complete recanalization was 75% but rate of near complete or complete recanalization was 41%. Reperfusion rates at angiography in the endovascular treatment group in IMS III trial [7] (TICI grades 2 or 3 indicating partial or complete re-perfusion) were 81% for an M1 occlusion but 65% for occlusion in the internal carotid artery, and 70% for a single occlusion in the M2 division of the MCA, A TICI score of 2b (partial reperfusion of half or more of the vascular distribution of the occluded artery) to 3, were 38% for an occlusion in the internal carotid artery, 44% for an occlusion in M1, and 44% for an M2 occlusion. If the rates of any recanalization on immediate post-procedure angiography were ≥80% (achieved in only patients with M1 segment MCA occlusion in IMS III [7]), the rates of favorable outcomes associated with endovascular treatment would have been in the range required to demonstrate a comparative benefit over IV alteplase.

An analysis of the IMS III trial [7] confirmed lack of recanalization as one of the major factors associated with absence of favorable outcome within the endovascular-treated cohort. The proportion of patients with an mRS of 0 to 2 at 90 days was 12.7% of the 55 patients with a TICI score of 0, in 27.6% of the 29 patients with a TICI score of 1, in 34.3% of the 108 patients with a TICI score of 2a (partial perfusion of less than half the vascular distribution of the occluded artery), in 47.9% of the 119 patients with a TICI score of 2b, and in 71.4% of the 7 patients with a TICI score of 3 ($P < 0.001$). If we assume the rate of patients with partial or complete recanalization increased from 126 (29%) to 217 (50%) with the use of any or combination of strategies (discussed in subsequent sections), the rate of mRS from 0 to 2 could have increased from 40.8% to 50%.

Reasons for less than optimal recanalization rates within recent trials

0.6 mg/kg versus 0.9 mg/kg IV alteplase prior to endovascular treatment

In the IMS III trial, [7] patients randomized to endovascular treatment were administered IV alteplase 0.6

mg/kg (bolus followed by infusion) followed by IA dose of 0 to 22 mg to keep the total alteplase dose to less than 0.9 mg/kg. Steady-state concentrations of alteplase ranging from approximately 2.2 to 3.3 μg/ml are considered optimal in treating acute MI [57,58]. Steady-state plasma concentrations of 0.9 to 1.6 μg/ml are reached with an IV alteplase dose of 0.6 mg/kg [59,60]. The steady-state concentration of 2.5 μg/ml can be achieved with an IV alteplase dose of 0.75 mg/kg [61]. Therefore, the effective steady state of alteplase concentration may not always be possible with IV alteplase doses of 0.6 mg/kg. There is some data to support a lower efficacy with 0.6 mg/kg dose compared with 0.9 mg/kg doses using IV alteplase. In one study, early recanalization of MCA occlusion was more frequent following 100 mg alteplase than 70 mg alteplase (34% vs. 25%), although the frequency of delayed recanalization did not differ (53% vs. 50%) [62,63]. A study found higher partial or complete recanalization rates with alteplase (duteplase) at the dose of 30 mega-international units [MIU]) (roughly 0.9 mg/kg) compared with 20 (roughly 0.6 mg/kg) or placebo [64](50% vs. 44% and 17%). Patients treated with 30 MIU alteplase showed significantly earlier and better clinical improvement, as measured by the neurologic scale, than did those treated with placebo. In another dose-comparison study [65] partial recanalization and complete recanalization were seen in 33.3% of patients administered 20 MIU and in 42.4% of patients administered 30 MIU, respectively.

The rationale of using 0.6 mg/kg of IV alteplase prior to endovascular treatment was to avoid using a total dose higher than 0.9 mg/kg of alteplase. In a pilot study, 94 patients received IV alteplase within 3 h of the onset of an acute ischemic stroke [66]. The doses tested ranged from 0.35 mg/kg to 1.05 mg/kg of alteplase. ICHs developed in 4 (18%) of 22 patients given an alteplase dose of at least 0.90 mg/kg versus only 1 hematoma in the remaining 72 patients (1%; $P <0.02$). There was no relation to the total dose of alteplase administered in milligrams. Parenchymal ICHs were seen in 20% of 307 patients treated with 1.1 mg/kg in ECASS I [67] and 12% of 407 patients treated with 0.9 mg/kg in ECASS II [68]. However, the 0.9 mg/kg alteplase dose was administered IV over 60 min in these trials and assumptions were carried forward to 0.9 mg/kg administered IV followed by IA treatment over approximately 4 h. The pharmacokinetics of alteplase are linear with low interindividual variation and rapid hepatic elimination [69]. The short half-life of alteplase (from 3 to 5 min) is expected to result in much lower bioavailability for the same total dose administered over 4 h versus over 1 h. Analysis of the relationship between total (IV + IA)

dose of alteplase and risk of symptomatic ICH in the IMS I and II trials did not demonstrate the same safety threshold findings as seen with pilot trials with IV alteplase. On June 27, 2011, the IV dose in the combined arm was increased from 0.6 mg/kg to 0.9 mg/kg and a combined maximum IV and IA total dose of 112 mg was defined as maximum dose in IMS III trial [7]. The possibility needs to be considered that if all patients randomized to endovascular treatment had received 0.9 mg/kg of IV alteplase prior to endovascular treatment, it could have improved the rates of recanalization.

A meta-analysis of 11 studies which included patients treated with IV alteplase followed by endovascular treatment was performed [18]. In 7 studies, 0.6 mg/kg IV alteplase had been administered to 317 patients, whereas 140 patients in 4 studies had received 0.9 mg/kg of IV alteplase. Symptomatic ICH was seen in 26 (8%) patients in the 0.6 mg/kg group compared with 10 (7%) of patients in the 0.9 mg/kg group [18]. The weighted mean of median NIHSS score at presentation was 18.3 in the 0.6 mg/kg group (median range from 9 to 34), and 17.3 in the 0.9 mg/kg group (median range from 4 to 39). Patients in the 0.9 mg/kg group had higher rates of favorable outcome [OR, 1.6, 95% CI 1.1 to 2.4, $P= 0.02$] and similar rates of symptomatic ICH [OR 0.9 (95% CI 0.4 to 1.8, $P= 0.7$]. Depending on the statistics used, the higher angiographic recanalization rate among patients treated with 0.9 mg/kg was significant ($P= 0.03$, events/trial syntax logistic regression) or borderline significant ($P= 0.07$, random effects model).

Dose of IA thrombolytics

IA alteplase in doses of 14 mg or less was allowed as a rescue therapy within 6 h after symptom onset in subjects recruited to the MR RESCUE [9] trial. Adjunctive IA alteplase was administered in eight patients (mean dose, 5.1 mg; range, 2 to 12). In the IMS III trial, [7] a maximum IA alteplase dose of 22 mg was administered over 2 h of infusion. A total of 266 of 434 patients randomized to endovascular treatment received IA alteplase. IA alteplase doses of 14 mg and 22 mg used in MR RESCUE [9] and IMS III, [7], respectively, would be considered low doses for IA thrombolytics. Further, IA alteplase dose is expected to be lower than that of IV alteplase to achieve similar results because of higher clot permeation, retention, and lysis (compared with IV alteplase) [70]. In studies involving acute arterial or venous occlusions involving the iliofemoral vasculature, 3 to 5 mg/h (for up to 12 h) of alteplase administered by IA route appears adequate to achieve therapeutic recanalization [71–75]. However, previous studies have used higher doses of IA alteplase ranging from 40 to 100 mg

in acute ischemic stroke patients with arterial occlusion [76–78].

There is preliminary data that doses greater than 20 mg of IA alteplase can produce additional recanalization in patients with acute ischemic stroke. In a pilot dose-escalation study of IA alteplase, [79] a maximum total dose of 40 mg of IA alteplase was administered. Angiograms were obtained after each 10 mg of alteplase. Mean perfusion grade improved from a pretreatment score of 0 with increasing doses of alteplase to 1.1 ± 1.0 with 10 mg, 1.5 ± 1.4 with 20 mg, 2.0 ± 0.8 with 30 mg, and 2.7 ± 1.0 with 40 mg. Mean thrombus degree decreased from a pre-treatment score of 4 with increasing doses of alteplase to 2.8 ± 1.2 after 10 mg, 2.6 ± 1.4 after 20 mg, 1.9 ± 1.5 after 30 mg, and 1.4 ± 1.5 after 40 mg. In the EMS Bridging Trial [35] 17 patients were randomized into the IV alteplase prior to receiving IA alteplase group and 18 into the IV placebo prior to IA alteplasegroup. The total alteplase dose was significantly greater in IV alteplase prior to receiving IA alteplasegroup (mean dose of 56.6 mg compared with 11.1 mg for the placebo and IA thrombolytic group, The recanalization rates as measured by TIMI score correlated to the total dose of alteplase given (correlation coefficient 0.36, $P= 0.05$). The mean alteplase dose given to patients with clot on initial angiogram and final flow of TIMI 0 was 20 mg but was 35.6 ± 21.4 mg for those with TIMI 1 flow, 38.6 ± 24.2 mg for those with TIMI 2 flow, and 56.7 ± 19.0 mg for those with TIMI 3 flow.

There is some data that demonstrates comparable rates of safety endpoints with IA alteplase doses greater than 20 mg. In one study, [2] the rates of safety endpoints associated with various doses of IA thrombolytics were evaluated. For standardization, a conversion factor for newer thrombolytics was established using a standard alteplase equivalent dosage (10 mg Alteplase = 2 Units of Reteplase = 6.3 Units of Tenecteplase). There was no relationship between increasing doses of IA thrombolytic (from 2 mg to 69 mg alteplase equivalent) and symptomatic or asymptomatic ICHs: ($P= 0.2$) and ($P= 0.7$), respectively. Another study evaluated the safety of high doses of urokinase (mean dose 200,000 U, range, from 25,000 to 1,500,000 U) and reteplase (mean 2 mg, range, from 1 to 8 mg or from 10 to 80 mg alteplase equivalent) for acute ischemic stroke after receiving IV alteplase [80]. Symptomatic ICH rates of 4.2% and 8.0% were observed with IA urokinase and reteplase, respectively. There was no correlation between symptomatic ICH and doses of urokinase and reteplase.

Alternatively, there is evidence that these extremely high doses of IA alteplase are counterproductive to effective thrombolysis. In the SYNTHESIS EXPANSION trial, [8] IA infusion of alteplase 0.9 mg/kg (maximum of 90 mg in the case of body weight ≥100 kg) over 1 h was to be performed. If a complete recanalization was achieved, the alteplase infusion could be interrupted before reaching the maximum dosage. The local concentration of thrombolytics and lysis of in vivo thrombus demonstrate a roughly bell-shaped dose–response curve [81,82]. There is an optimal concentration that result in 80% clot lysis and eightfold higher or sixfold lower concentrations than optimal concentration reduce lysis by approximately 50% [83]. This phenomenon is attributed to local attrition of plasminogen termed as "plasminogen steal." There is no data that has identified the optimal concentration of alteplase for local thrombolysis in the setting of ischemic stroke.

Mechanical thrombectomy as a sole treatment

Mechanical thrombectomy as a sole treatment strategy for achieving angiographic recanalization was used in IMS III and MR RESCUE trials. In the IMS III trial, [7] mechanical thrombectomy alone was used in 68 of 434 patients randomized to endovascular treatment. In the MR RESCUE trial, [9] 56 of 64 patients assigned to undergo embolectomy received only mechanical thrombectomy. There is, however, evidence that indicates that mechanical thrombectomy alone is an inferior strategy to mechanical thrombectomy with IA thrombolytic administration. The MERCI 1 study [84] reported successful recanalization with mechanical embolectomy alone in 43% of 30 patients, and with additional IA thrombolytic administration in 64% of patients. In the subsequent MultiMERCI trial, mechanical thrombectomy alone resulted in successful recanalization in 54% of 111 patients and rates increased to 69% after adjunctive IA thrombolytic administration [85]. The rate of post-procedural ICH was not different between patients treated with mechanical thrombectomy and those treated with a combination of mechanical thrombectomy and pharmacological thrombolytics. A post-hoc comparison [86] reported higher recanalization rates in patients who were treated with pharmacological and mechanical modalities compared with those treated with mechanical thrombectomy (76.9% vs. 68.6%).

Another retrospective comparison of IA tenecteplase with mechanical thrombectomy and mechanical thrombectomy alone (included primary angioplasty or stent placement) was performed in patients who received endovascular treatment for acute ischemic stroke [2]. The median NIHSS score (range) was 15 (5 to 25) and 14 (5 to 25) in patients treated with IA tenecteplase with mechanical thrombectomy and mechanical thrombec-

tomy alone, respectively. The rates of favorable outcome (mRS 0 to 2) at 30 days/discharge were higher in patients treated with IA tenecteplase with mechanical thrombectomy compared with mechanical thrombectomy alone (45% vs. 27%, and OR = 3.0, 95% CI .97 to 9.5, $P = 0.06$). There was no difference in the rates of asymptomatic or symptomatic ICHs. In another study evaluating 75 patients with intracranial internal carotid artery occlusion, the highest recanalization rates were observed with MERCI embolectomy combined with IA thrombolytics (86%) [78]. IA thrombolytics alone and MERCI embolectomy alone achieved 18% and 46.2% recanalization rates, respectively.

There is also evidence that re-occlusion may be higher in patients who are treated with mechanical thrombectomy alone [87,88]. The use of mechanical disruption (such as balloon angioplasty, snare manipulation, or stent placement) may lead to disruption of atherosclerotic plaques or endothelial erosion that triggers platelet activation, adherence and aggregation. There is exposure of tissue factor, which, in turn, activates the clotting cascade. A retrospective analysis of data from 4 prospective acute stroke protocols [89] found that acute re-occlusion was seen in 3 of 19 patients treated with mechanical thrombectomy alone and none of 13 patients treated with IA reteplase and IV abciximab. In another study, subacute re-occlusion (at 24 h) was seen in 5 of 56 patients with ischemic stroke treated with endovascular treatment [90,91]. The rate of subacute re-occlusion was higher with mechanical thrombectomy alone compared with IA thrombolytics and mechanical thrombectomy (2/6 vs. 3/50).

Lack of third generation IA thrombolytic use

Alteplase was the only thrombolytic medication that was used in IMS III, [7] SYNTHESIS EXPANSION, [8] and MR RESCUE trials [9] which is a second generation plasminogen activator with a short half-life (from 3 to 5 min) and limited penetration due to strong binding with surface fibrin [92]. However, third generation plasminogen activators such as reteplase and tenecteplase have higher fibrin specificity and penetration into thrombus and longer half-lives [93]. There is some data supporting a higher therapeutic efficacy of 0.1 mg/kg or 0.25 mg/kg of tenecteplase (compared with alteplase) in patients treated within 6 h of ischemic stroke onset selected by a perfusion lesion on CT perfusion imaging [93]. Both the two tenecteplase groups had greater reperfusion on perfusion-weighted MRI and clinical improvement at 24 h than the alteplase group. The higher dose of tenecteplase (0.25 mg/kg) was superior to alteplase for all efficacy outcomes, including absence of serious disability at 90

days. In another study of 13 patients with MCA occlusions treated and resistant to IV alteplase, a second bolus of IV tenecteplase (0.1 mg/kg) resulted in completed recanalization in all patients [94]. In another study, [2] borderline statistical significance was seen toward favorable functional outcome (mRS of 0 to 2) at 1 month in the IA tenecteplase-treated patients compared with patients treated with other thrombolytics/thrombectomy alone.

Another third generation thrombolytic, IA reteplase, has gained prominence due to higher rates of recanalization (compared with IA alteplase) in retrospective studies [95]. An indirect comparison with PROACT II [13] suggested a higher rate of partial or complete recanalization associated with the use of IA reteplase with or without angioplasty than with IA prourokinase without angioplasty (94% vs. 66%). Another comparison of 33 patients who received IA reteplase and 22 patients receiving IA urokinase found higher recanalization rates with IA reteplase (82% vs. 64%) [96]. Therefore, the possibility cannot be excluded that use of third generation thrombolytics as part of endovascular treatment could have resulted in higher recanalization rates.

Limited use of new generation thrombectomy devices (stent retrievers)

The rapid evolution in technology is also evident in thrombectomy devices. In this regard, FDA approved of the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) concentric retriever (Concentric Medical, Mountain View, CA) in August 2004 and the Penumbra system (Penumbra, Alameda, CA) in January 2008. Subsequently, newer generation of MERCI concentric retriever (L5) was introduced. The Multi MERCI trial [97] reported higher rates of recanalization with newer generation thrombectomy devices compared with the first generation (57.3% and 45.5% of cases in which newer generation L5 and older generation X5/X6 devices were used, respectively).

In 2012, the FDA approved two new devices: the Trevo Pro and Solitaire stent retrievers [98]. The SOLITAIRE™ with the intention for thrombectomy (SWIFT) trial, [99] randomized ischemic stroke patients treated within 8 h of symptom onset to receive thrombectomy treatment with either the SOLITAIRE™ Flow Restoration device or Merci. A higher rate of partial or complete recanalization (without symptomatic ICH) was seen with thrombectomy using SOLITAIRE™ compared with Merci (61% vs. 24%, OR 4.9, $P < 0.0001$). A higher rate of favorable outcomes at 3 months was seen in Solitaire treated than with Merci-treated patients

(58% vs 33%; OR 2.8, *P*= 0.0001). The Trevo versus Merci retrievers for thrombectomy revascularization of large vessel occlusions in acute ischemic stroke (TREVO 2) trial [100] randomized ischemic stroke patients treated within 8 h of symptom onset to thrombectomy with Trevo (n=88) or Merci devices (n=90). A higher rate of partial or complete recanalization was seen with thrombectomy using Trevo compared with Merci (86% vs. 60%, OR 4.2, *P* < 0.0001). Another single center study found that successful recanalization was achieved in 82% of patients treated with stent retrievers compared with 62% of patients treated with Merci retrievers [101]. Subsequently, mRS of 0 to 2 was seen at 90 days in 65% of patients treated with stent retrievers and 35% of those treated with the Merci device. Patients treated with stent retrievers also have a significantly shorter procedure time compared with Merci retriever devices [101]. Procedure time may be an important determinant of clinical outcome [102]. In one study, [102] patients with procedure time ≤30 min had lower rates of unfavorable outcome at discharge compared with patients with procedure time ≥30 min (52.3% vs. 72.2%).

In the IMS III trial, [7] Solitaire was used in 5 of 434 patients randomized to endovascular treatment. In the SYNTHESIS EXPANSION trial, [8] Solitaire (EV3/ Covidien), and Trevo (Concentric/ Stryker) were used in 23 of the 181 patients assigned to endovascular treatment. In MR RESCUE, [9] no patient was treated with Solitaire or Trevo retriever. The low rates of Solitaire or Trevo use in all the above mentioned studies could partially explain the relatively low rates of partial or complete recanalization seen in these studies.

Detection and magnitude of benefit and clinical trial design

Imbalances between treatment groups

Different methods of treatment allocation for multi-center and/or stratified randomized clinical trials can result in substantial differences between the characteristics of patients allocated to each treatment arm [103]. This may lead to a bias in the result or raise the possibility of an investigator-introduced selection bias. The concern is most prominent in trials with small sample sizes [104–106]. A critical review of MR RESCUE [9] demonstrates higher rates of IV alteplase use (44% vs. 30%) and ICA occlusion (20% vs. 13%) in patients randomized to embolectomy treatment. The rates of congestive heart failure (8% vs. 26%) and MI (16% vs. 26%) were significantly lower among patients randomized to embo-

lectomy treatment. The relatively lower frequency of adverse prognostic factors in the embolectomy group may have reduced the chances of detecting a meaningful difference between embolectomy and standard treatment in the randomized patients. The median NIHSS score was lower in patients with favorable penumbral pattern in both embolectomy and standard treatment groups, thus confounding the comparison between patients with favorable and non-favorable penumbral patterns.

In the SYNTHESIS EXPANSION trial, [8] the rate of underlying atrial fibrillation was significantly lower in patients randomized to endovascular treatment (8% vs. 16%). The rate of underlying dissections was significantly higher in patients randomized to endovascular treatment (8% vs. 2%). The prognostic value of atrial fibrillation in patients with ischemic stroke receiving IV alteplase has been discussed in previous sections but data indicates that atrial fibrillation may be an important determinant of rates of worsening at 7 days and poor outcome (mRS >3 and death) at 3 months [47]. A disproportionately higher rate of dissections can bias towards an asymmetrically higher rate of poor outcomes. Several studies have demonstrated a high rate of death and disability in thrombolytic-treated patients who have acute ischemic stroke secondary to arterial dissections [107–109]. Furthermore, stent placement is considered a reasonable adjunct to IV or IA thrombolytic in acute ischemic stroke patients with dissection [110,111] which was not permissible in the SYNTHESIS EXPANSION trial [8].

In the IMS III trial, [7] the proportion of patients with baseline mRS of 2 to 3 were higher in patients randomized to endovascular treatment compared with IV alteplase alone (6% vs. 2%). The history of coronary artery disease was less frequent in patients randomized to endovascular treatment (24% vs. 32%). The impact of these imbalances in IMS III is, however, expected to be small.

Choice of primary endpoints

In the IMS III trial, [7] the primary outcome was defined by proportion of subjects with an mRS of 0 to 2 at 90 days. The primary outcome was defined by proportion of subjects with a mRS of 0 or 1 at 90 days in the SYNTHESIS EXPANSION [8] trial. The difference in mean scores on the mRS was the primary outcome in the MR RESCUE [9] trial. There is little agreement where mRS data should be divided (i.e., 0,1 vs. 2 to 6, 0 to 2 vs. 3 to 6, or 0 to 3 vs. 4 to 6) or should mRS be analyzed as an ordinal variable. There is some evidence that point of dichotomization makes a difference in achieving statisti-

cal significance or clinical interpretation. In a retrospective analysis of the ECASS I trial, intention-to-treat data set (615 randomized and treated patients), efficacy analysis was not significant using a comparison of medians (the primary analysis) between IV alteplase and placebo-treated subjects [102]. The differences between IV alteplase and the placebo-treated group achieved borderline significance if favorable outcome was defined by mRS from 0 to 1 at 3 months ($P= 0.044$). The primary efficacy analysis in ECASS II was not significant using a comparison of a dichotomous outcomes (comparison of mRS from 0 to 1 vs. 2 to 6) [112] but demonstrated benefit of IV alteplase (over placebo) with an analysis using a different dichotomization point (mRS from 0 2 vs. 3 to 6) or with a bootstrap analysis [113]. In an analysis of 47 trials including 54,173 patients, [114] multiple methods of comparative analysis were assessed for sensitivity in detecting differences between intervention and placebo groups in rates of clinical endpoints. The rate of identifying a statistically significant difference was as follows: mRS 0 to 1 versus 2 to 6 (9.3%), 0 to 5 versus 6 (11.8%), and 0 to 2 versus 3 to 6 (21.8%) and ordinal logistic regression (25.9%).

Based on the above mentioned studies, analyzing the data using fixed dichotomous analysis of mRS as in IMS III [7] and SYNTHESIS EXPANSION [8] is less likely to demonstrate therapeutic benefit compared with analyzing mRS as an ordinal variable [115]. However, in the IMS III trial, [7] pre-specified secondary analyses showed no significant differences between the two treatment groups when mRS was used as an ordinal variable ($P = 0.25$). In the SYNTHESIS EXPANSION trial, [8] the proportion of patients with an mRS of 0 or 1 at 3 months was 30.4% with endovascular treatment and 34.8% with IV alteplase. If the outcome of mRS from 0 to 2 was used, the proportion of patients was 42% with endovascular treatment and 46% with IV alteplase. In the MR RESCUE [9] trial, 19% of patients randomized to embolectomy and 20% of patients randomized to standard treatment had an mRS of 0 to 2. Therefore, choice of a different endpoint was unlikely to demonstrate any different results as confirmed by secondary analysis in these studies.

Sample size estimation

In the IMS III trial, [7] a sample size of 900 subjects (2:1 ratio) was based on the assumption that the proportion of patients with primary outcome (mRS from 0 to 2 at 3 months) will be 40% in the IV alteplase group. Endovascular treatment was anticipated to increase the proportion of patients with primary outcome to at least 50% (absolute increase of 10%) in IV alteplase followed

by endovascular treatment group [116]. The sample size provided *alpha* of 0.05 and power of 80% for detecting difference in binomial proportions (two-tailed test). The sample size of 900 included inflation by 1.03 to safeguard against dilution of the effect size by patients lost to follow-up and/or treatment cross-over in approximately 1–3% of the cases. The proportion of patients who achieved mRS from 0 to 2 in 161 subjects recruited in IMS I and II and treated with IV alteplase followed by endovascular treatment was 71 (44%). The proportion of patients who achieved mRS from 0 to 2 in 182 IV alteplase alone treated subjects with similar characteristics recruited in NINDS rt-PA trial (serving as historical controls) was 71 (39%) [116]—an absolute difference of only 5%. Therefore, the pilot data was not supporting the concept that the magnitude of benefit (10% or greater) sought in the IMS III trial [7] was possible.

In the SYNTHESIS EXPANSION trial, [8] the estimated sample size of 344 (1:1 ratio) was based on the assumption that the proportion of patients with primary outcome (mRS at 0 to 1 at 3 months) will be 40% in the IV alteplase group. Endovascular treatment was anticipated to increase the proportion of patients with primary outcome to at least 55% (absolute increase of 15%) [117]. The sample size provided *alpha* of 0.05 and power of 80% for detecting difference in binomial proportions (two-tailed test). An absolute increase of 15% in proportion of patients achieving primary outcome among patients treated within 4.5 h after symptom onset was greater than the increase seen with IV alteplase (over placebo) among patients treated within 3 h (13% absolute increase) [10] and those treated between 3 and 4.5 h (7% absolute increase) [11] after symptom onset. Therefore, unless the magnitude of benefit was going to be much greater than that demonstrated in previous trials, the trial was unlikely to reject the null hypothesis. Conversely, the trial was underpowered to detect differences of smaller magnitude that may be clinically meaningful.

In the MR RESCUE trial [9], the assumption was that the mean mRS values at 3 months in patients with favorable penumbral pattern treated with embolectomy will be 3.05 and 4.6 in those treated with the standard treatment. Among the embolectomy group, the mean mRS values will be 3.05 and 4.45 in patients with and without favorable penumbral pattern on neuroimaging [9]. The sample size of 30 patients in each of the four groups provided alpha of 0.05 for statistical comparisons. The trial was seeking a relative reduction of approximately 33% in mean mRS scores in patients treated with embolectomy in the presence of favorable penumbral pattern

Table 2. A summary of recommendations pertaining to neuroimaging in patients with acute ischemic stroke and anticipated changes

Recommendations according to AHA/ASA guidelines[123]	Level of evidence	Anticipated change
1. Either CT or MRI is recommended before IV rt-PA administration to exclude ICH (absolute contraindication) and to determine whether CT hypodensity or MRI hyperintensity of ischemia is present	Class I[†]†; Level of Evidence A	None
2. IV fibrinolytic therapy is recommended in the setting of early ischemic changes (other than frank hypodensity) on CT, regardless of their extent	Class I; Level of Evidence A	None
3. A non-invasive intracranial vascular study is strongly recommended during the initial imaging evaluation of the acute stroke patient if either IA fibrinolysis or mechanical thrombectomy is contemplated for management but should not delay IV rt-PA if indicated	Class I; Level of Evidence A	None
4. CT perfusion and MRI perfusion and diffusion imaging, including measures of infarct core and penumbra, may be considered for the selection of patients for acute reperfusion therapy beyond the time windows for IV fibrinolysis. These techniques provide additional information that may improve diagnosis, mechanism, and severity of ischemic stroke and allow more informed clinical decision making.	Class IIb; Level of Evidence B	May be modified based on MR RESCUE trial

Note: *AHA* American Heart Association; *ASA* American Stroke Association; *CT* computed tomography; *MRI* magnetic resonance imaging; *IA* intra-arterial; *IV* intravenous; *rt-PA* recombinant tissue plasminogen activator

[†]Class I-Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective.

Class II-Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.

Class IIa-The weight of evidence or opinion is in favor of the procedure or treatment.

Class IIb-Usefulness/efficacy is less well established by evidence or opinion.

Class III-Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful.

Level of evidence

A-Data derived from multiple randomized clinical trials.

B-Data derived from a single randomized trial or non-randomized studies.

C-Consensus opinion of experts.

compared with either standard treatment group or embolectomy in the absence of favorable penumbral pattern on neuroimaging. The magnitude of relative reduction required to reject null hypothesis was quite high. Furthermore, the small sample size cannot assure that the data from the two samples are both normally distributed, and the SDs from the two samples are approximately equal [118]. Therefore, appropriate transformation of the data was required before performing any calculations. Since MR RESCUE [9] analysis required multiple comparisons, adjustment methods were to further reduce the possibility of detecting statistically significant differences [119].

Recommendations from professional organizations

Existing recommendations

The 2003 guidelines by the Stroke Council of the American Stroke Association (ASA) [120] concluded that the IA administration of at least one specific thrombolytic agent appears to be of some benefit in the treatment of carefully selected patients with acute ischemic stroke secondary to occlusion of the MCA (level I). The Brain Attack Coalition [121] recognized that there has been extensive experience with endovascular treatment, which is commonly used at many medical centers and is recommended in the current American Heart Association (AHA) *Advanced Cardiac Life Support* handbook.

Based on all of these factors and the consensus of the Brain Attack Coalition, endovascular treatment of acute ischemic stroke was considered a recommended component of a comprehensive stroke center (grade IIB). The 2007 guideline from the American Stroke Association Stroke Council [122] additionally recommended that treatment requires the patient to be at an experienced stroke center with immediate access to cerebral angiography and qualified interventionalists. Endovascular treatment was considered reasonable in patients who have contraindications to use of intravenous thrombolysis, such as recent surgery (Class IIa, Level of Evidence C). The AHA/ASA 2013 guidelines [123] have made recommendations prior to publication of IMS III, [7] SYNTHESIS EXPANSION, [8] and MR RESCUE [9] trials which are summarized in Tables 4 and 5.

Anticipated changes in guidelines

Tables 2 and 3 summarize the recommendations and anticipated changes pertaining to neuroimaging and endovascular treatment, respectively. As can be seen from these tables, the anticipated changes are few and none of them is anticipated to be Class I (conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective) or Class III (conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful).

Table 3. A summary of recommendations pertaining to endovascular treatment in patients with acute ischemic stroke and anticipated changes

Recommendations according to AHA/ASA guidelines[123]	Level of evidence	Anticipated change
1. Intravenous rt-PA (0.9 mg/kg, maximum dose 90 mg) is recommended for administration to eligible patients who can be treated in the time period of 3 to 4.5 h after stroke onset with the following additional exclusion criteria: patients >80 years old; those taking oral anticoagulants regardless of INR; those with a baseline NIHSS score >25, those with imaging evidence of ischemic injury involving more than one third of the MCA territory, or those with a history of both stroke and diabetes mellitus.	Class I; Level of Evidence B	None
2. Patients eligible for intravenous rt-PA should receive intravenous rt-PA even if IA treatments are being considered.	Class I; Level of Evidence A	None
3. IA fibrinolysis is beneficial for treatment of carefully selected patients with major ischemic strokes of <6 h duration caused by occlusions of the MCA who are not otherwise candidates for intravenous rt-PA.	Class I; Level of Evidence B	None
4. Time from symptom onset to reperfusion with IA therapies is highly correlated with better clinical outcomes, and all efforts must be undertaken to minimize delays to definitive therapy.	Class I; Level of Evidence B	None
5. IA treatment requires the patient to be at an experienced stroke center with rapid access to cerebral angiography and qualified interventionalists. An emphasis on expeditious assessment and treatment should be made. Facilities are encouraged to define criteria that can be used to credential individuals who can perform IA revascularization procedures. Outcomes on all patients should be tracked.	Class I; Level of Evidence C	None
6. When mechanical thrombectomy is pursued, stent retrievers such as Solitaire FR and Trevo are generally preferred to coil retrievers such as Merci.	Class I; Level of Evidence A	None
7. IA fibrinolysis or mechanical thrombectomy is reasonable in patients who have contraindications to the use of IV rt-PA.	Class IIa; Level of Evidence C	None
8. Rescue IA fibrinolysis or mechanical thrombectomy may be reasonable approaches to recanalization in patients with large-artery occlusion who have not responded to intravenous fibrinolysis. Additional randomized trial data are needed.	Class IIb; Level of Evidence B	None
9. The Merci, Penumbra System, Solitaire FR, and Trevo thrombectomy devices can be useful in achieving recanalization alone or in combination with pharmacological fibrinolysis in carefully selected patients. Their ability to improve patient outcomes has not yet been established.	Class IIa; Level of Evidence B	None

Note: *AHA* American Heart Association; *ASA* American Stroke Association; *NIHSS* National Institutes of Health Stroke Scale; *INR*, internationalized normalized ratio; *MCA*, middle cerebral artery; *IA*, intra-arterial; *IV*, intravenous; *rt-PA*, recombinant tissue plasminogen activator

The role of CT perfusion and MR perfusion and diffusion imaging is classified as Class II; Level of Evidence B (conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment) in current guidelines. The results of MR RESCUE [9] are unlikely to shift the current recommendation.

In the 2013 guidelines, rescue IA fibrinolysis or mechanical thrombectomy may be reasonable approaches to recanalization in patients with large-artery occlusion who have not responded to IV thrombolysis. Additional randomized trial data are needed. The recommendation is classified as Class II; Level of Evidence B which is unlikely to shift into Class III due to lack of definitive data within IMS III [7] for this subgroup of patients. In the 2013 guidelines, IA thrombolysis or mechanical thrombectomy was considered reasonable in patients who have contraindications to the use of intravenous fibrinolysis. Neither the IMS III [7] nor SYNTHESIS EXPANSION [8] provided any new data for this subgroup of patients. Therefore, the recommendations will probably remain unchanged.

The recommendation that IA thrombolysis was beneficial for treatment of carefully selected patients with major ischemic strokes of <6 h duration caused by occlusions of the MCA who are not otherwise candidates for intravenous alteplase may require further consideration. IMS III, [7] SYNTHESIS EXPANSION, [8] and MR RESCUE [9] trials all included patients with MCA occlusions. The recanalization rates appeared to be the highest in IMS III [7] and MR RESCUE [9] for MCA occlusions. However, unless post-hoc analysis is able to conclusive demonstrate lack of benefit, the level of evidence may remain unchanged as Class I; Level of Evidence B.

New guidelines required for optimizing time to treatment

The IMS III, [7] SYNTHESIS EXPANSION, [8] and MR RESCUE [9] trials have all demonstrated prominent delays in triage and initiation of endovascular treatment in acute ischemic stroke patients. The lack of efficiency with stroke systems is partly attributable to paucity of recommendations regarding optimal time intervals for *ED* arrival to microcatheter placement within AHA/ASA Stroke Council acute ischemic stroke guidelines [123]. The AHA Special Writing Group of the Stroke Council Metrics [124] recommended tracking the median time from arrival to start of endovascular treatment for acute ischemic stroke patients as metrics in measuring quality of care in Comprehensive Stroke Centers.

Although no optimal time period is provided, a time interval of <90 min to define optimal performance may be considered based on the time interval recommenda-

tions of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines in treatment of acute MI [125]. The guidelines recommend a door to balloon time of <90 min for percutaneous coronary intervention in patients with acute MI. However, the patients with acute MI present with an EKG performed by Emergency Medical Services (EMS) confirming the MI diagnosis but the confirmation of acute ischemic stroke occurs after CT scan acquisition. Therefore, an appropriate matching surrogate for door to balloon time is CT scan to microcatheter time in patients with ischemic stroke [126]. A time interval of <120 min to define optimal performance with regard to ED arrival to microcatheter time may be considered to account for the additional 30 min that are permissible in regards to door to CT scan time consistent with the recommendations of the National Symposium on Rapid Identification and Treatment of Acute Stroke [127] and Brain Attack Coalition [128]. An international writing group composed of all societies that treat stroke using endovascular methods recommended door to groin puncture of 120 min in their Multisociety Consensus Quality Improvement Guidelines for Intraarterial Catheter-directed Treatment of Acute Ischemic Stroke [129]. Furthermore, these guidelines mandated tracking of the standard clinical outcomes (mRS at 90 days).

Regulatory approval and reimbursement for procedure after IMS III, SYNTHESIS EXPANSION, and MR RESCUE trials

Regulatory approvals

MERCI concentric retriever (Concentric Medical, Mountain View, CA) and the Penumbra system (Penumbra, Alameda, CA) were approved in August 2004 and January 2008, respectively, for use in revascularization in patients with acute stroke within 8 h of symptom onset as discussed in previous sections. In 2012, the FDA approved two new stent based retrievers for similar indications**:** Solitaire FR Revascularization Device (Covidien), approved March 2012 and Trevo Pro Retriever (Stryker Corp.) approved August 2012 [98]. The current approval of each of the devices is likely to continue.

Reimbursement for procedure

Endovascular treatment of acute ischemic stroke is reimbursed through a prospective payment system called Medicare Severity Diagnosis Related Groups (MS-DRGs) to reimburse hospitals for inpatient stays. Each inpatient stay is assigned to an MS-DRG that is determined according to the principal diagnosis, major procedures, discharge status, and complicating secondary diagnoses. With acute ischemic stroke (occlusion with infarct) as the principal diagnosis and endovascular removal of an obstruction of head/neck vessels as the primary procedure, patients may be assigned to MS-DRG 23 or 24 [130,131]. MS-DRG 23 is defined as craniotomy with major device implant or acute complex CNS PDX with MCC (*major complication or comorbidity*) and MS-DRG 24 as craniotomy with major device implant or acute complex CNS PDX without MCC. The MS-DRG is assigned a flat payment rate, which is adjusted according to the individual hospital's teaching status, disproportionate share services for treating low-income, uninsured and/or underinsured patients, and location in urban versus rural regions. Other health insurers may reimburse hospitals for inpatient care using per diem rates, DRGs, case rates, or a percentage of charges. Some health insurers may also provide separate payment for single-use disposable devices, such as the Merci Retrieval System®, used in endovascular mechanical embolectomy/thrombectomy procedures.

These DRGs represent hospitalization associated with any of the multiple designated procedures and therefore any change in re-imbursement based on these DRG codes is unlikely. In addition, since endovascular treatment of patients with acute ischemic stroke is consistent with the guidelines in certain settings as described above, the re-imbursement is likely to continue. It is possible that documentation of certain criteria for patient selection may be required and in the absence of such documentation, the claim may be denied. The hospital will either have to provide the required documentation during audit or re-assign the patients to DRG 559, 14, or 15 as deemed appropriate.

The professional fees is in addition to the MS-DRG payment and is based on CPT (Current Procedural Terminology) codes associated with this procedure which include 37184, 36216, 36217, 36218, 75680, 75671 75685, 75685 to 59, and +75774. By definition, code 39.74 is assigned for procedures using mechanical methods of removing an embolus or thrombus, including the Merci Retrieval System. This code is specifically used for an endovascular approach. It includes the pre-cerebral vessels in the neck, such as the common carotid artery, and the cerebral (intracranial) vessels of the head, such as the middle cerebral artery. Since the procedure is considered appropriate in certain circumstances according to the Stroke Council of ASA/AHA, the CPT codes will remain valid for purposes of claiming professional fees.

The next step after IMS III, SYNTHESIS EXPANSION, and MR RESCUE trials

It is likely that endovascular treatment will continue to be offered at most institutions. However, it would be of paramount importance to ensure that outcomes are tracked and reliably ascertained [132]. Such methods require ascertainment of procedure-related adverse events that could be ascertained reliably and compared with rates observed in previous practice-defining clinical studies. For example, the rates of symptomatic ICHs in 533 patients treated with endovascular treatment in PROACT I, [5] PROACT II [13], IND 9180 [6] MERCI [14] MultiMERCI [85], EMS, [35] IMS, [56] Multi-MERCI [85] (post-IV alteplase) was 47 (8.8%, 95% CI 6.4 to 11.2%). If the rates of symptomatic ICHs exceed the upper limit of 95% CI, the institution should perform a thorough evaluation of patient selection with appropriate adjustment for clinical severity, if required.

The consent forms for the procedure either as part of the registry or outside the registry may require documentation that the patient or legally authorized representative was informed regarding the results of the IMS III, [7] SYNTHESIS EXPANSION, [8] and MR RESCUE [9] trials and the reasons for expected benefit of endovascular treatment in the current scenario to the consenting party. An objective and reliably ascertained peri-procedural rate of symptomatic ICHs and favorable outcomes at the local institution can be invaluable during the consenting process.

As mentioned in the previous sections, the number of acute ischemic stroke patients with basilar artery occlusion in the recent trials was too small for any valid conclusions regarding the role of endovascular treatment in this patient population. One of the trials to address the gap in scientific data is the Basilar Artery International Cooperation Study (BASICS) [133] which is a randomized controlled, multicenter, open label, phase III intervention trial with blinded outcome assessment. The trial will investigate the efficacy and safety of additional endovascular treatment after IV alteplase in 750 patients with basilar artery occlusion confirmed by CT or MR angiography. Patients will be randomized between additional or no additional endovascular treatments. IV alteplase has to be initiated within 4.5 h from estimated symptom onset and endovascular treatment within 6 h. The primary outcome will be favorable outcome at day 90 defined by an mRS score of 0 to 3.

Members of the writing group are of the opinion that IMS III, [7] SYNTHESIS EXPANSION, [8] and MR RESCUE [9] trials did not support a large magnitude benefit of endovascular treatment in subjects randomized in all three trials. The possibility that benefits of a smaller magnitude exist in certain patient populations cannot be excluded. Large magnitude benefits can be expected with implementation of "parameter optimized endovascular treatment" in patients with ischemic stroke who are candidates for IV thrombolytics. Members of the writing group support continuation of endovascular treatment in acute ischemic stroke patients in settings where "parameter optimized endovascular treatment" can be consistently performed.

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