Abstract—Acute ischemic stroke (AIS) is a devastating disease constituting the fifth leading cause of death in the United States. Effectively treating AIS has always been a challenge in clinical practice as neural cells are vulnerable to ischemic insults and susceptible to anoxic damage. Since the FDA approval of intravenous (IV) thrombolysis with tissue plasminogen activator (tPA), treatment of AIS has changed significantly. Accumulated evidence over the past two decades in clinical practice indicated that IV tPA has been proven to be an effective regimen for AIS with acceptable safety profile up to 4.5 hours after the onset of symptoms. Furthermore, efforts have been made on searching for alternative or adjunctive therapies to IV tPA. Clinically emerged intra-arterial intervention with promising outcomes has become a feasible option for patients who are ineligible for IV thrombolysis or have failed in recanalization of a large occluded vessel. Although it has been contentious in respect to whether endovascular therapy truly improves outcome in the treatment of AIS, evidence from the most recently published results of randomized controlled endovascular intervention trials is quite encouraging. This review outlines some practical milestones in the development of effective treatments for AIS.

Keywords — acute ischemic stroke, endovascular intervention, intra-arterial thrombolysis, intravenous tissue plasminogen activator, mechanical thrombectomy, tPA.
year, which counts to one stroke every 40 seconds on average (1). Early reperfusion is an urgent priority in acute stroke treatment. The successful restoration of blood flow serves as the most powerful predictor of stroke outcome. Tissue plasminogen activator (tPA) is so far the only thrombolytic agent approved by FDA in the US for AIS treatment. Intravenous tPA (IV tPA) has been proven to be beneficial for AIS patients if given within 4.5 hours after stroke onset (3). Alternatives to IV tPA, including tenecteplase and desmoteplase, are still under investigation (4, 5). As an adjunctive therapy to IV tPA, applying transcranial ultrasound onto occluded vessels, namely sonothrombolysis, was found to potentiate thrombolytic efficacy (6, 7). Due to the limitations of IV tPA in acute stroke management, catheter-based intra-arterial (IA) interventions including IA thrombolysis and mechanical thrombectomy have been under active investigation for the last two decades. However, the efficacy and safety concerns associated with endovascular therapy have been a constant debate along the way. Only until recently, randomized controlled trials began to show the net benefit on functional outcome with IA intervention. In this article the authors review important milestones in AIS treatment based on the findings from carefully selected clinical trials.

III. CURRENTLY CLINICAL AVAILABLE TREATMENT OPTIONS FOR ACUTE ISCHEMIC STROKE

Intravenous tPA

Intravenous administration of tPA was approved in 1996 by FDA in the US based on the NINDS trial (8). Subsequently, it was also approved by Canada in 1999 and Europe in 2002 (9). The therapeutic benefits of tPA have been confirmed by several large scale randomized placebo-controlled clinical trials (8, 10-12), and meta-analyses (3, 13), which demonstrate a favorable physical outcome at 3 to 6 months (measured as modified Rankin Score [mRS] 0-1) with acceptable risk of intracranial hemorrhage when IV tPA is given within 4.5 hours after stroke onset, irrespective of age or stroke severity (13). Further analysis demonstrated a direct relationship between the time and treatment effect – the sooner the IV tPA treatment initiated, the better the clinical outcome ensured, especially if started within 90 min of stroke onset (14, 15). Saver and colleagues quantified the concept using MRI-based infarct volumetrics, i.e. with every passing minute until reperfusion, 1.9 million neurons and 14 billion synapses are lost, pointing out “time is brain” (16). A recent study of 58,353 tPA-treated patients also highlighted that for every 15-minute improvement in time-to-treatment, patients were less likely to die and more likely to be ambulatory at discharge (17). These findings underscore the importance to accelerate hospital presentation and thrombolytic treatment in patients with AIS. IV tPA treatment has been recommended in the guideline by the American Heart Association (AHA) and American Academy of Neurology (AAN), and an arrival to treatment initiation (door-to-needle) time of less than 60 minutes is encouraged (18). However, despite such supporting data, IV tPA remains substantially underutilized. Challenges to the widespread use of IV tPA include: i) The net benefit would be faded when IV tPA is given beyond the 4.5-hour time window (3). ii) Certain contraindications limit its use, such as recent surgery or stroke, previous intracranial hemorrhage, or coagulopathy abnormalities (18). iii) IV tPA is not effective towards a large or lengthy clot. Clinical observations have shown that, 2 hours after IV tPA, the complete recanalization rate could be achieved in 44.2% of the distal middle cerebral artery (MCA) occlusion, 30% of the proximal MCA while only 5.9% of the terminal internal carotid artery (19). Among those with complete or partial recanalization, up to one third may proceed with re-occlusion (20). If the thrombus exceeds 8 mm in length, there is nearly 0% of chances of recanalization with IV tPA (21). iv) Inadequate amount of neurological and stroke expertise available in the community. Research is ongoing to improve efficacy of tPA through more rapid stroke diagnosis and treatment, refinement of advanced neuroimaging and stroke biomarkers, and successful demonstration of alternative means in promoting reperfusion. Education to both the medical community and general public is a sure path to facilitate the use of IV tPA in eligible candidates to improve the outcomes of AIS patients.

Several more potent fibrinolytic agents as alternatives to tPA have been introduced, including tenecteplase and desmoteplase. Tenecteplase is a genetically modified form of tPA, while desmoteplase is a distinct protease found in the saliva of a blood-feeding vampire bat. Both possess much greater fibrin specificity, longer half-lives, and can be used as a single bolus, conferring the potential to induce faster and more complete clot lysis with a widened time window beyond 4.5 hours and less bleeding complications (22, 23). However, recent randomized clinical trials in AIS patients comparing either tenecteplase vs. tPA or desmoteplase vs. placebo have yielded mixed results (24-28), and further clinical studies on efficacies of these agents for AIS are still under investigation (29, 30).

Sonothrombolysis

As an adjunctive therapy of IV tPA, employing continuous ultrasound sonication targeting an arterial occlusive clot, namely sonothrombolysis, in order to facilitate the fibrinolytic effect of IV tPA, has gained clinical interest. The mechanism by which sonothrombolysis enhances the clot-dissolving capabilities of IV tPA has been believed by delivering acoustic pressure to the target brain vessel. CLOTBUST (Combined Lysis Of Thrombus in Brain ischemia using transcranial Ultrasound and Systemic TPA) trial demonstrated that combination of tPA with 2 hours of transcranial Doppler (TCD) rendered higher rates of recanalization in patients with AIS when compared to those treated with IV tPA alone (6). Notably, no increase in symptomatic intracerebral hemorrhage was observed. Furthermore, trends toward better clinical outcomes at 24 hours and 3 months were also noticed in the sonothrombolysis group. Molina and colleagues reported in a phase IIb TUCSON (Transcranial Ultrasound in Clinical SONothrombolysis) trial in which combination of gaseous microspheres, TCD and tPA was associated with higher recanalization rates and better clinical recovery scores (7). Independent meta-analyses have also confirmed that sonothrombolysis was able to reduce death or dependency at 3 months and to increase recanalization without augmenting the risk of symptomatic intracranial hemorrhage (31). However,
larger scale clinical trials are warranted to validate the sonothrombolytic effect. Currently, a phase III trial is undergoing using an operator-independent ultrasound device to eliminate the requirement of neurosonology training (32).

**Intra-arterial (IA) treatment**

Cases of ineffective IV tPA thrombolysis, particularly in AIS patients with a large vessel occlusion (LVO) or contraindicated with IV tPA, are frequently encountered. It is reasonable to explore whether an alternative approach may improve therapeutic outcomes, such as employing a catheter-based arterial intervention directly targeting on the occlusion. Earlier clinical trials seemed to support this hypothesis. A randomized-controlled trial, PROACT II (PROlyse in Acute Cerebral Thromboembolism II) conducted in Europe, showed that intra-arterially administrating prourokinase up to 6 hours from symptom onset significantly increased MCA recanalization rate measured as TIMI (Thrombolysis in Myocardial Infarction) grade 2 to 3 (66% vs. 18%) and associated with better clinical outcomes at 3 months (mRS 0-2) compared with IV heparin, despite higher incidence of intracranial hemorrhage (10% vs. 2%) (33). However, clinical use of IA prourokinase for AIS treatment was never approved by FDA in the US. Instead, devices for mechanical thrombectomy, such as the first-generation MERCI and PENUMBRA, have become popular in clinical use after FDA 510(k) clearance when IV tPA is ineligible or refractory within 8 hours after the symptom onset due to a LVO. Clinical trials using MERCI device showed that the recanalization rates (TIMI 2 to 3) were 46% to 57.3%, and can be improved to 69.5% if combined with IA tPA (34, 35). Symptomatic intracranial hemorrhage rates (7.8% to 9.8%) were comparable to those in PROACT II, while the clinically significant procedural complications ranged from 5.5% to 7.1%. Employing PENUMBRA aspiration system achieved a higher recanalization rate (TIMI 2 to 3, 82% to 87%) than did the MERCI device, but was adversely associated with higher rates of symptomatic intracranial hemorrhage (11.2%) and procedural events (5.7% to 12.8%) (36, 37). Using either device, favorable clinical outcomes with mRS 0-2 at 90 days (25% to 46%) were proportionally associated with the successful recanalization (38, 39). The major drawback in these trials was the single-arm prospective design without concurrent controls; therefore, the clinical efficacy of these devices is yet to be established. While clinicians were still waiting for large randomized controlled trials to be conducted for the first-generation devices, the second-generation stent retrievers, Solitaire and TREVO, have quickly surfaced. In two randomized clinical trials published in 2012, the SWIFT (Solitaire With the Intention For Thrombectomy) trial and the TREVO 2 (Thrombectomy REvascularization of Large Vessel Occlusion) trial, these stent retrievers were compared with the MERCI device in AIS patients (NIHSS 8-30) due to LVO not responding, or ineligible to IV tPA within 8 hours of ictus (40, 41). A significant higher recanalization rate (TIMI 2 to 3, 69% vs. 30%), better physical outcome at 90 days (58% vs. 33%), and lower mortality rate (17% vs. 38%) were observed in Solitaire group. Similarly, TREVO group was found to have substantial higher successful recanalization rate measured as TICI (Thrombolysis in Cerebral Infarction) score 2b to 3 (68% vs. 44%), while no difference in mortality rate compared with the MERCI group at 90 days. In a prospective non-randomized study, patients with proximal MCA occlusions treated with the Solitaire device resulted in more favorable 90-day physical outcomes (mRS 0-2) compared with IV tPA (60% vs. 37.5%) (42). A recent review on the safety and efficacy of mechanical thrombectomy with Solitaire stent retrieval for AIS stated that the Solitaire stent is effective and safe with a high recanalization rate and low procedural complications (43). Employing these devices for thrombectomy in carefully selected AIS patients (Class IIa; Level of Evidence B) as urgent management has been recommended in 2013 AHA/ASA (American Stroke Association) guideline (18).

However, controversies exist. In 2013 three long-expected randomized controlled trials published in the New England Journal of Medicine argued for no benefit of endovascular procedures over medical treatment alone for AIS (44-46). IMS III (Intervention Management of Stroke III) trial enrolled 656 AIS patients within 3 hours of onset who were randomized into the groups of endovascular therapy after IV tPA and of IV tPA alone (45). The trial showed a similar safety profile in outcomes (90-day mortality and intracranial hemorrhage within 30 hours) and no significant difference in functional independence (mRS 0-2) between these two groups. However, this study had several limitations. First, only 47% of the enrolled patients had cerebral vascular imaging at the time of enrollment, leading to approximately 20% patients enrolled in the intervention group had no LVO or accessible thrombus during the procedure. Importantly, subgroup analysis showed the 90-day outcomes (mRS 0-2) were significantly better with IA intervention in patients with LVO. Second, only the first-generation device was used for thrombectomy in the majority of the subjects, in whom the recanalization (TICI 2b-3) rate was only approximately 40%, which could be improved with the use of the second-generation device.

The second study, SYNTHESIS Expansion trial, included 362 patients with AIS whom were randomized into the group of IV tPA within 4.5 hours after onset or the group of IA endovascular therapy within 6 hours of onset (either IA tPA, or mechanical thrombectomy, or both) groups (46). In this trial, no statistical significance was found in either safety (intracranial hemorrhage or death within 7 days) or physical outcome (mRS 0-1 at 3 months) between these two groups. It is not surprising that the median time from stroke onset to the start of treatment was significantly longer for the endovascular therapy group than for the IV tPA group (3.75 vs. 2.75 hours). Notably, 10% subjects randomized to the endovascular group had no thrombus on subsequent neuroimaging, but received IA tPA to a suspected territory. Of the patients who were confirmed with thrombus on following angiography in the endovascular group, only approximately one third of patients received mechanical thrombectomy in addition to IA tPA; however, no recanalization rate was reported.
The MR RESCUE (Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy) trial investigated whether a favorable penumbral pattern on neuroimaging would benefit AIS patients from acute endovascular treatment within 8 hours of stroke onset (44). In this trial, 118 patients with confirmed anterior LVO (with or without IV tPA) were randomly assigned into four subgroups according to the type of treatment (thrombectomy vs. standard care) and penumbral pattern (favorable vs. unfavorable). Results from this trial indicated that favorable penumbral patterns identified on imaging did not benefit patients from endovascular therapy, nor was thrombectomy superior to standard care in AIS. However, critics have argued that only first-generation thrombectomy devices were used, and the successful recanalization rate (TICI 2b-3) was only 27% which was much less than that of using the second-generation devices. Nonetheless, in a subgroup analysis, patients with reperfusion showed a lower mean 90-day mRS (P=0.04) and a smaller absolute infarct volume (P<0.001), emphasizing the importance of recanalization.

Taken together, the negative results from the aforementioned three randomized controlled trials have pointed out the uncertainty regarding the efficacy of the catheter-based endovascular approach. The common criticisms against these three trials included the absence of a confirmation of pre-treatment LVO, limited use of second-generation mechanical devices resulting in low recanalization rate, and relatively long intervals before the initiation of IA endovascular treatment. Therefore, appropriate selection of the patients, use of the second-generation devices, and prompt initiation of IA endovascular treatment are paramount regarding future clinical trial design. Published in 2014, MR CLEAN (Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands) trial fulfilled these criteria, and came up first with convincing evidence to show a benefit of IA approach vs. the current standard care on functional outcomes in treating AIS (47).

In the MR CLEAN trial, 500 AIS patients with confirmed LVO in anterior cerebral circulation on vessel imaging were randomized into the groups of standard care plus IA endovascular intervention vs. standard care alone. The IA endovascular intervention was defined as consisting of IA thrombolysis with tPA or urokinase, mechanical treatment or both. Mechanical treatment refers to retraction, aspiration, wire disruption, or use of a retrievable stent (stent retriever). A majority of patients (89%) had received IV tPA before randomization and the median time from stroke onset to IV thrombolytic agent was less than 90 minutes. The intervention was performed within 6 hours after symptom onset, and second-generation mechanical devices (stent retriever) were employed in 97% subjects who received IA therapy. As expected, the intervention positively influenced all clinical and imaging outcomes. A shift was seen in the distribution of the mRS in favor of the intervention, consistent in all categories of the scale, except for death (adjusted common odds ratio [OR]: 1.67, 95% confidence interval [CI]: 1.21-2.30). 13.5% more patients were functionally independent (mRS 0-2) in the intervention group than in the control group (32.6% vs. 19.1%, adjusted common OR: 2.16, 95%CI: 1.39-3.38). The NIHSS score after 5-7 days was on average 2.9 points (95% CI: 1.5-4.3) lower than in the control group. Absence of residual
occlusion at the target sites, as assessed by CT angiogram after 24 hours, was more common in the intervention group (75.4%, [141/187] vs. 32.9% [68/207]). Infarct volume was smaller after the intervention, with a between-group difference of 19 ml (95% CI: 3-34). In terms of safety outcomes, no difference was seen between the two groups in the frequency of serious adverse events during the 90 days of follow-up. No difference in mortality was seen at 7, 30 or 90 days, and the observed effect was consistent across all predefined subgroups. In addition, subgroup analysis showed benefits from IA treatment also extended to elderly patients who were older than 80 years old. This is in disagreement with previous belief that, in patients over 80 years of age, the chances of gaining functional independence after endovascular recanalization seem to be limited (48). Moreover, MR CLEAN trial has demonstrated that applying endovascular therapy to AIS patients produced universal benefits from mild (NIHSS 2-10) to severe (NIHSS >20) stroke when administered within 6 hours after stroke onset, arguing against the previous opinion that mild symptoms do not justify endovascular therapy (49). An additional analysis in an abstract presented during the International Stroke Conference in February 2015 showed the absolute difference in functional independence (mRS 0-2) between the intervention and standard treatment alone groups were 33% in those reperfused by 2 hours and only 6.5% in those reperfused after 6 hours, an estimated 7% decrease in every additional hour from stroke onset to reperfusion (50), reiterating the old slogan – “Time Is Brain”.

In light of the positive results from MR CLEAN, four similar interventional trials were subsequently stopped because of efficacy after early interim analyses showed benefit in the intervention group. Results from three of the four trials, including ESCAPE (Endovascular treatment for Small Core and Anterior circulation Proximal occlusion with Emphasis on minimizing CT to recanalization times), EXTEND IA (EXTending the time for Thrombolysis in Emergency Neurological Deficits with Intra-Arterial therapy), and SWIFT PRIME (Solitaire FR With the Intention For Thrombectomy as PRIMary Endovascular treatment for acute ischemic stroke) were most recently presented at the International Stroke Conference in Nashville, TN, in February of 2015, while the report from REVASCAT (Revascularization with Solitaire FR device versus best medical therapy in the treatment of acute stroke due to anterior circulation large vessel occlusion presenting within eight-hours of symptoms onset) will be unveiled at the European Stroke Organization Conference in April (52). All three trials, ESCAPE (53), EXTEND IA (54), and SWIFT PRIME (55), shared similar study design as MR CLEAN (Table 1). Subjects were 1:1 randomized into medical treatment plus intervention vs. medical treatment only groups with confirmed anterior circulation LVO on neuroimaging. Inclusion criteria also required good pre-stroke physical function, IV tPA to be given within 4.5 hours for eligible patients and the intervention to be started within 6 hours, although ESCAPE allowed enrolling patients up to 12 hours delay in reperfusion (51), reiterating the old slogan – “Time Is Brain”.

<table>
<thead>
<tr>
<th>TABLE II</th>
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<tr>
<td><strong>COMPARISON OF PATIENT CHARACTERISTICS AMONG FOUR RECENT ENDOVASCULAR TRIALS</strong></td>
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<table>
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<tr>
<th></th>
<th>MR CLEAN</th>
<th>ESCAPE</th>
<th>SWIFT PRIME</th>
<th>EXTEND IA</th>
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<tbody>
<tr>
<td>Mean age (years) – median/mean</td>
<td>65.8/65.7</td>
<td>71.7/70.0</td>
<td>65.0/66.3</td>
<td>68.6/70.2</td>
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<tr>
<td>Male (%)</td>
<td>57.9/58.8</td>
<td>61.8/61.5</td>
<td>55.1/46.9</td>
<td>49/49</td>
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<tr>
<td>White (%)</td>
<td>82.3/87.3</td>
<td>88.8/90.2</td>
<td>71.7/73.7</td>
<td>7.1/7.6</td>
</tr>
<tr>
<td>Pre-stroke mRS 2+ (%)</td>
<td>9.5/10.0</td>
<td>81/90</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>NIHSS score - median</td>
<td>17/18</td>
<td>16/17</td>
<td>16/17</td>
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<tr>
<td>NIHSS mRS – median/mean</td>
<td>146/145</td>
<td>147/146</td>
<td>150/148.5</td>
<td>150/150.5</td>
</tr>
<tr>
<td>DBI (mm/H) – median/mean</td>
<td>6.6/6.7</td>
<td>7.4/7.3</td>
<td>7.1/7.6</td>
<td>7.6/7.8</td>
</tr>
<tr>
<td>ASPECTS – median</td>
<td>9/9</td>
<td>9/9</td>
<td>9/9</td>
<td>9/9</td>
</tr>
<tr>
<td>Site of occlusion</td>
<td>Intracranial ICA (%)</td>
<td>0.4/1.1</td>
<td>4.3/4.3</td>
<td>31/#</td>
</tr>
<tr>
<td>Carotid terminus (%)</td>
<td>22.3/28.2</td>
<td>27.6/26.5</td>
<td>10.0/11.7</td>
<td>10.0/11.7</td>
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<tr>
<td>M1 MCA (%)</td>
<td>66.1/62</td>
<td>68.2/71.4</td>
<td>67.7/77.7</td>
<td>57/51</td>
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<tr>
<td>M2 MCA (%)</td>
<td>7.7/7.9</td>
<td>3.7/2.0</td>
<td>14.0/6.4</td>
<td>11/17</td>
</tr>
<tr>
<td>A1 or A2 (%)</td>
<td>0.4/0.8</td>
<td>0.0/0.0</td>
<td>0.0/0.0</td>
<td>0.0/0.0</td>
</tr>
<tr>
<td>Ipsilateral cervical carotid occlusion (%)</td>
<td>32.2/26.3</td>
<td>21/19</td>
<td>34/32</td>
<td>32/32</td>
</tr>
<tr>
<td>Carotid stent required (%)</td>
<td>15/15</td>
<td>15/15</td>
<td>15/15</td>
<td>15/15</td>
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<tr>
<td>Use of general anesthesia (%)</td>
<td>38/38</td>
<td>39/39</td>
<td>39/39</td>
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<tr>
<td>Use of retrievable stents (%)</td>
<td>81.5 (190/233)</td>
<td>78.8 (130/165)</td>
<td>100 (100/100)</td>
<td>100 (100/100)</td>
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<tr>
<td>IV tPA received (%)</td>
<td>87.1/90.0</td>
<td>72.7/78.7</td>
<td>100/100</td>
<td>100/100</td>
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<tr>
<td>Onset to IV tPA (min) - median</td>
<td>85/87</td>
<td>110/125</td>
<td>110/117</td>
<td>127/145</td>
</tr>
<tr>
<td>Onset to randomization (min)</td>
<td>204/186</td>
<td>169/172</td>
<td>188.5</td>
<td>188.5</td>
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<tr>
<td>Onset to groin puncture (min)</td>
<td>260/260</td>
<td>51/51</td>
<td>58/58</td>
<td>58/58</td>
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<tr>
<td>Image to groin puncture (min)</td>
<td>51/51</td>
<td>58/58</td>
<td>58/58</td>
<td>58/58</td>
</tr>
<tr>
<td>Groin puncture to first reperfusion (min)</td>
<td>30/30</td>
<td>29/29</td>
<td>29/29</td>
<td>29/29</td>
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<tr>
<td>Groin puncture to final reperfusion (min)</td>
<td>241/241</td>
<td>241/241</td>
<td>241/241</td>
<td>241/241</td>
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</table>

# - including extracranial ICA
$ - percentage of stent retriever used among patients who were randomized into intervention group
$$ - percentage of stent retriever used among patients who underwent endovascular intervention
from symptom onset. Unlike MR CLEAN, these trials included additional imaging criteria to selectively identify patients with small infarct core and large ischemic penumbra. At the time of trial termination, ESCAPE enrolled total 315 AIS patients, SWIFT PRIME 196, and EXTEND IA 70. All subjects in SWIFT PRIME and EXTEND IA as well as about 80% in ESCAPE received IV tPA, and the median time from onset to IV tPA ranging from 110 to 145 min. The majority of patients in the intervention group (100% in SWIFT and EXTEND IA as well as 75% in ESCAPE) received second generation stent retriever. Although patients in these three trials waited longer for IV tPA administration compared with those in MR CLEAN, the median time from onset to reperfusion was just approximately 4 hours, much faster than that in MR CLEAN trial (Table 2).

Following MR CLEAN’s footsteps, the recently reported results from these three endovascular trials once again convincingly demonstrated an even more robust benefit on functional recovery favoring intervention in AIS patients, confirming MR CLEAN’s findings (Table 3). All three trials showed the same pattern of significant downward shift in mRS with the intervention, carrying an adjusted common odd ratio between 2 to 3.1, higher than 1.67 seen in MR CLEAN. The absolute risk reduction (ARR) for independency at 90-day post stroke (mRS 0-2) between intervention group and control group was greater in these trials than in MR CLEAN (23.7-31% vs. 13.5%), which was translated into a smaller number needed to treat (NNT, 3.2-4.2 vs. 7.4). Higher successful recanalization rates (TICI 2b-3, ranging from 72.4% to 88%) comparing with that of MR CLEAN (58.7%) was another highlight in these studies. The use of neuroimaging to select patients, shorter time window from onset to reperfusion, and improved rates of angiographic revascularization were the key factors that account for the higher proportions of independent functional outcomes and the larger effect sizes observed in these trials in contrast to MR CLEAN, despite comparable clinical severities and demographic characteristics. Similar to MR CLEAN, the beneficial effects in these studies run the gamut of all prespecified subgroups, including age, gender, ASPECTS, NIHSS at baseline, location of occlusion, with or without IV tPA, as well as time from onset to randomization. These three trials unanimously demonstrated that endovascular therapy is a safe procedure to perform in AIS patients with LVO. There was significant reduction of 90-day mortality in ESCAPE and a clear trend of decreased death rate in EXTEND IA and SWIFT PRIME associated with intervention group vs. control group (Table 3). No significance was noticed for symptomatic intracranial hemorrhage, subarachnoid hemorrhage or severe adverse effects. However, IA manipulation is known to be associated with an increased risk of procedure-related embolic events. In ESCAPE, 4.9% (8/165) subjects in the intervention group suffered from recurrent stroke compared to only 2% (3/150) in the control group (53). Similarly, 5.7% (2/35) subjects in intervention group from EXTEND IA had evidence of embolization into new vascular territories (54). These findings echoed those in MR CLEAN where 8.6% (20/233) of the patients in endovascular group had embolization into new vascular territories. Among them, 5.6% (13/233) was
symptomatic vs. only 0.4% (1/267) in the control group, highlighting an increased risk of catheter-based procedures for new embolic stroke (47).

Taken together, the most recent trials, ESCAPE, EXTEND IA, and SWIFT PRIME, have validated the findings of MR CLEAN, speaking against the arguments of uncertainty from the previous studies of IMS III, SYNTHESIS, and MR RESCUE. The key elements for success in IA intervention include presence of a confirmed LVO, usage of a stent retriever, and ensuring the rapid achievement of reperfusion in appropriately selected patients. However, it was arguable that only a small proportion of AIS patients may be eligible for the IA intervention given the strict selection criteria, thereby limiting its broad utilization. Additionally, endovascular capabilities are only readily available in a handful of comprehensive stroke centers. Effectively improved inter-hospital transfer using modern modalities such as a helicopter (drip-and-ship method) available in many small- to medium-sized hospitals may facilitate earlier endovascular treatment for AIS patients (56). In spite of limitations, the conclusions from these trials are long-awaited breakthroughs that will significantly impact the manner of our current clinical practice and set up another milestone in AIS management as what IV tPA did two decades ago. It redeems a big step towards employing endovascular intervention as a vital component in acute stroke care protocol in the near future.

IV. SUMMARY

Effectively managing AIS patients remains a challenging task which motivates clinicians to search for better means. The milestone that IV tPA became clinically available has changed the way that AIS was previously managed for the past twenty years. Today, findings from these positive endovascular trials may serve as another milestone in AIS management as what IV tPA did two decades ago. It redeems a big step towards employing endovascular intervention as a vital component in acute stroke care protocol in the near future.

References

Questions (please choose one single answer):

1. Which of the following descriptions regarding IV tPA in acute ischemic stroke management is incorrect?
   a. IV tPA is not recommended to give beyond 4.5-hour time window.
   b. Contraindications limits the use of IV tPA.
   c. IV tPA tends to be less effective for large clot.
   d. IV tPA tends to be less effective for lengthy clot.
   e. Recanalization rate by IV tPA is more effective in proximal MCA than distal MCA.

2. Which one of the following trials provided the first convincing evidence of benefits of endovascular approach vs. the current standard care on functional outcomes in treating acute ischemic stroke?
   a. ESCAPE.
   b. IMS III.
   c. MR CLEAN.
   d. MR RESCUE.
   e. SWIFT PRIME

3. Which of the following intra-arterial (IA) procedures or devices have been approved by FDA in AIS treatment in the USA?
   a. MERCI or PENUMBRA.
   b. SOLITAIRE or TREVO.
   c. IA tPA
   d. All of above.
   e. None of above.

Correct answer: 1: e; 2: c; 3: e (explain: all are clinically available but are still considered as experimental)