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Improving Reperfusion Therapies in the Era of Mechanical Thrombectomy

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Abstract

Recent positive clinical trials using mechanical thrombectomy proved that endovascular recanalization is an effective treatment for patients with acute stroke secondary to large vessel occlusions. The trials offer definite evidence that in acute ischemia recanalization is a powerful predictor of good outcome. However, even in the era of rapid and effective recanalization using endovascular approaches, the percentage of patients with good outcomes varies between 33% and 71%. In addition, the number of patients who are eligible for endovascular thrombectomy is small and usually based on having salvageable tissue on imaging. There is therefore room for improvement to both enhance the effectiveness of current practice and expand treatment to a larger subset of stroke patients. In this review, we highlight some of the most promising approaches to improve endovascular therapy by combining with strategies to enhance collateral perfusion and vascular protection.

Keywords

Endovascular thrombectomy; acute stroke; neuroprotection; tissue plasminogen activator; intra-arterial delivery

Introduction

Acute ischemic stroke secondary to large vessel occlusion (LVO) is a common and devastating condition resulting in death and disability in a high proportion of patients. Over the last 2 decades, we progressed from an era of observation and mostly supportive care to an era of time- and imaging-guided acute recanalization of the occluded artery by endovascular thrombectomy (ET). Using latest generation technology 5 multicenter, controlled, randomized, clinical trials (MR CLEAN, ESCAPE, EXTEND IA, SWIFT-PRIME and REVASCAT) showed superiority of the endovascular approach over medical management for acute LVO [1-5]. However, in these trials despite high rates of complete

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recanalization by ET, there remained a subset of patients that had poor outcome [1-5]. It is therefore worth considering novel strategies for improving outcome from LVO in the era of rapid and effective ET.

In addition to the progress in acute recanalization, basic science research has made considerable progress in unraveling the complexity of pathophysiological events occurring after occlusion of a major cerebral artery. In addition, by examining the mechanisms playing a role in CBF changes and the ischemic cascade, basic and preclinical studies have revealed several promising therapeutic targets for treatment of acute stroke. However, although promising, neuroprotective agents have failed in phase II/III clinical trials [6,7]. Because neuroprotective agents are not likely to be efficacious without a vascular route needed to reach the target tissue, they are not likely to be beneficial in the absence of rapid recanalization of the occluded artery. Lack of a vascular route and incomplete reperfusion of downstream tissues may be some of the reasons behind the failure of neuroprotection in obtaining good outcomes in clinical trials for ischemic stroke in the pre-ET era.

To date, the target of all neuroprotective agents has been the ischemic penumbra, a region of constrained blood supply that is potentially salvageable if recanalization occurs rapidly or neuroprotective agents are present to prevent cell death [7-9]. However, not all patients have salvageable tissue on CT prior to recanalization and are therefore not good candidates for ET. In the era of rapid and effective ET, treatment that can prevent collateral failure or even open existing collaterals combined with ET-induced reperfusion may open the door to treating more patients effectively. In addition, the new generation of devices and advances in ET may allow for selective intra-arterial (IA) delivery of drugs or manipulation of CBF in relatively small vascular territories. IA treatment with ET may provide promising new approaches to improve outcome from LVO by enhancing reperfusion and limiting secondary injury such as edema and hemorrhage. The purpose of this review is to discuss the advancement in ET for acute stroke treatment and highlight some of the most promising potential approaches and targets for improved reperfusion therapies.

Recanalization as a predictor of good outcome for acute ischemic stroke

The first major clinical step showing that recanalization of the occluded vessel was a powerful predictor of good outcome was the NIH/NINDS intravenous (IV) tissue plasminogen activator (tPA) trial [10]. The trial confirmed the important concept of time-sensitive revascularization in acute ischemic stroke. Subsequently, the endovascular approach was pioneered as treatment for acute LVO. The first 3 clinical randomized trials of endovascular approach in LVO (SYNTHESIS Expansion, IMS III and MR RESCUE) failed to demonstrate superiority of the endovascular approach over standard IV tPA therapy [11-13]. There were several drawbacks in these trials, in particular the use of first generation thrombectomy devices that likely prevented them from showing benefit because of extended time needed for revascularization. Using latest generation technology, MR CLEAN, ESCAPE, EXTEND IA and SWIFT-PRIME, and REVASCAT, 5 multicenter, controlled, randomized, clinical trials showed superiority of the endovascular approach over medical management for acute LVO [1-5]. The following is a brief review of the design and outcome from the 5 successful ET trials.

Multicenter Randomized Clinical Trial of Endo-vascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN)

MR CLEAN was a randomized controlled trial of eligible acute stroke patients to either endovascular intervention plus standard medical management versus medical management only [1]. Inclusion criteria were patients with a proximal anterior circulation LVO within 6 hours after symptom onset. Primary outcome was 90 day modified Rankin Scale (mRS). The treatment effect was estimated with ordinal logistic regression over the entire range of the mRS score (shift analysis). The investigators randomized 500 patients in 16 medical centers, 233 were randomized to ET and 267 to standard medical care that included IV tPA. Retrievable stents were used in 190 of the 233 patients (81.5%) assigned to IA treatment. In the endovascular arm, 32.6 % of patients had a mRS ≤ 2 at 90 days compared to 19.1% in the medical management arm. In the trial, there was an absolute difference of 13.5 percentage points (95% CI, 5.9 to 21.2) in the rates of patients with mRS < 2 (0 to 2) in favor of the intervention (32.6% vs. 19.1%). With regards to safety, there were no significant differences in the rates of symptomatic intracerebral hemorrhage (ICH) or mortality between the two groups.

Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE)

The ESCAPE trial was a multicenter, prospective, randomized, open label, controlled trial with blinded outcome evaluation (PROBE design) [2]. Eligible stroke patients were randomized 1:1 to receive endovascular treatment or guideline-based care alone (control group). Inclusion criteria were patients with a proximal, intracranial, anterior circulation LVO within 12 hours after symptom onset. In addition to the clinical inclusion criteria, ESCAPE had an imaging component. In fact, patients with a large infarct core assessed by the Alberta Stroke Program Early Computed Tomography Score (ASPECTS) score or poor collateral circulation on CT angiography were excluded from randomization. Importantly, the ESCAPE operators were encouraged to reach pre-determined time targets from CT to groin and CT to recanalization. The trial was stopped early because the interim analysis demonstrated “overwhelming superiority” of the endovascular approach over medical management. In particular, in 22 centers worldwide, the investigators enrolled 316 patients of which 238 received IV tPA with 120 included in the endovascular arm and 118 in the control arm. In the endovascular arm, median time from CT to first reperfusion was 84 minutes. Rate of “functional independence” (mRS ≤ 2) was increased by mechanical thrombectomy (53.0%, vs. 29.3% in the control group; P<0.001). The median 90-day was mRS 2 in the intervention group and 4 in the control group (P<0.001). Mortality was lower in patients who underwent mechanical thrombectomy (10.4%, vs. 19.0%; P=0.04).

Extending the Time for Thrombolysis in Emergency Neurological Deficits — Intra-Arterial (EXTEND-IA)

EXTEND-IA was a multicenter, prospective, randomized, open-label, with blinded end-point trial of patients treated with IV tPA as criteria for randomization [3]. In particular, the investigators selected acute ischemic stroke patients who received standard 0.9 mg/kg of IV tPA within 4.5 hours after symptom onset. These patients were then subsequently

randomized to mechanical thrombectomy with stent retriever or IV tPA alone. As inclusion criteria EXTEND IA included LVO or anterior circulation occlusions. In addition, the trial had as inclusion criteria evidence of ischemic core of less than 70 ml on CT perfusion imaging. As primary outcomes, the investigators selected reperfusion at 24 hours and early neurologic improvement indicated by ≥8-point reduction on the NIHSS or a score of 0 or 1 at day 3. Secondary outcomes included the functional score on mRS at 90 days. Similar to ESCAPE, EXTEND-IA had an interim analysis triggered by the results of MR CLEAN. After analyzing the data, the Data Monitoring Safety Board (DSMB) decided to halt the trial for overwhelming efficacy of ET after only 70 patients were randomized.

The percentage of patients who were functionally independent (i.e., mRS ≤ 2 at 90 days) was 71% in the endovascular arm. This rate of functional independence was the highest of all trials. In addition, early neurologic improvement at 3 days was extremely high in patients treated with mechanical thrombectomy compared to IV tPA (80% vs. 37%, P=0.002). With regards to perfusion imaging, the ischemic core underwent successful revascularization resulting in decrease in the growth of the ischemic core at 24 hours. This was greater in the endovascular group compare to the IV tPA group (median, 100% vs. 37%; P<0.001). Similar to MR CLEAN and ESCAPE, in EXTEND-IA there were no significant differences in rates of death or symptomatic ICH between patients treated with mechanical thrombectomy versus standard IV tPA.

Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME)

SWIFT PRIME was an international, multicenter, prospective, randomized, open clinical trial, that compared acute stroke patients treated with IV t-PA compared to patients treated ET in conjunction with IV t-PA [4]. The trial was also stopped early because of efficacy. In 39 centers, 196 patients underwent randomization. Thrombectomy plus IV t-PA was superior to IV tPA alone for disability over the entire range of the mRS at 90 days. In addition, the proportion of patients with functional independence (mRS ≤ 2) was higher in the ET group compared to controls (60% vs. 35%, P<0.001). With regards to safety, there were no significant differences between 90-day mortality (9% vs. 12%, P=0.50) or symptomatic ICH between the two groups (0% vs. 3%, P=0.12).

Randomized Trial of 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 Symptom Onset (REVASCAT)

REVASCAT was a multicenter, prospective, randomized, sequential, open-label phase III trial with blinded evaluation [5]. In the trial, the investigators treated patients with acute ischemic stroke within 8 hours after the onset of symptoms. Patients received either medical therapy (including IV t-PA when eligible) and ET (thrombectomy group) or medical therapy alone (control group). Similarly to SWIFT PRIME, ET reduced the severity of disability over the range of the mRS. In the trial, ET led to higher rates of functional independence (mRS ≤ 2) at 90 days (43.7% vs. 28.2%). In terms of safety, there was no difference in rates of symptomatic intracranial hemorrhage and death between the groups.

The role of collaterals and the ischemic penumbra in acute stroke treatment with ET

The recent positive ET trials described above reinforced the concept that rapid reperfusion of the ischemic brain is a powerful predictor of good outcome [1-5]. These trials also highlight that the greatest benefit was in those patients that had salvageable tissue on imaging. For example, in ESCAPE and EXTEND-IA trials, patients were excluded if they had a large ischemic core or poor collateral circulation based on CT angiography. The approach of selecting patients with robust collateral circulation as candidates for ET was based a large body of literature showing that: 1) the presence of robust collateral circulation has been shown to be a strong predictor for good outcomes after recanalization; 2) patients with good collaterals at stroke onset have better reperfusion rates, smaller infarcts, and less hemorrhagic transformation; and 3) patients with poor collaterals have low recanalization rates and poor outcomes even if recanalization is achieved [14,16,18-21].

The importance of collaterals in acute stroke is not just for clinical decision making and is not unique to ET. It is generally accepted that the ischemic penumbra is maintained by secondary collaterals that connect distal branches of major cerebral artery territories [22,23]. After MCA occlusion, the leptomeningeal anastomoses (LMA) between the MCA and anterior cerebral artery (ACA) vascular territories can sustain flow enough to keep neurons alive sometimes for hours beyond the treatment window of IV tPA [22,23]. Thus, LMA vessels are incredibly important in this regard as their size and number directly impact flow to the penumbral tissue and therefore slowing the enlargement of the ischemic core [24]. Collateral perfusion has been attributed to passive increases in flow from the unobstructed to the obstructed vascular territory. However in an isolated vessel preparation it has recently been shown that LMAs of chronically hypertensive rats were highly vasoconstricted and displayed considerable pressure-induced myogenic tone [25]. This was in contrast to LMAs from normotensive rats that were larger and more passive, a state that would be conducive to bidirectional flow [25]. The significance of this finding is that chronic hypertension is well-known to be associated with poor outcome from ischemic stroke due to increased perfusion deficit and limited penumbral tissue [26-28]. That pial collaterals are vasoconstricted during hypertension - as opposed to structurally smaller - importantly suggests that LMAs can be opened to sustain or create penumbral flow to extend the time window for treatment. In addition, the potential to open vasoconstricted LMAs in stroke patients with poor collateral flow could increase the number of patients eligible for ET.

Potential targets for collateral opening

One approach to opening vasoconstricted pial collaterals is pharmacologic inhibition of rho-associated protein kinase (ROCK). ROCK is expressed and active in numerous cell types including vascular smooth muscle, endothelium, neurons, glia and immune cells [29]. Abnormal activation of ROCK is thought to have a key role in numerous pathologies, including hypertension, diabetes and atherosclerosis, conditions known to have poor outcome from stroke [30-33]. Stroke injury is also linked to ROCK activation through hemodynamic and microvascular dysfunction as well inflammation and oxidative stress [34-38]. Numerous animal studies have shown that inhibition of ROCK improves stroke

outcome in normal as well as diseased animals, likely through several mechanisms including augmenting collateral flow [35-40]. ROCK has also been shown to be involved in myogenic vasoconstriction [41], making it a potentially important and unique target to open collaterals.

Other potential targets for opening collaterals are the small- and intermediate-conductance calcium-activated potassium (SK and IK) channels. SK and IK channels are expressed only in cerebral endothelium and cause vasodilation through endothelium-dependent hyperpolarization (EDH) [44]. EDH is not basally active in large pial arteries, but is considered a backup vasodilator to nitric oxide (NO) under disease conditions when NO is inhibited or bioavailability is decreased [44]. In contrast, brain parenchymal arterioles have been shown to constrict in response to SK and IK channel inhibition, suggesting EDH is basally active in these small arterioles [25]. Recently, LMAs were shown to constrict to IK but not SK channel inhibition, suggesting basal IK channel activity that inhibits tone in pial collaterals. Although selective IK channel activation will likely dilate all cerebral arteries and arterioles, the sensitivity difference between the small arterioles and large arteries may make IK channel activation at low doses an effective means to open collaterals. Activation of IK channels as a vascular therapeutic is not a new concept and has been shown to improve coronary blood flow in both males and females [45].

NO donors are also potential targets for opening collaterals and are currently being tested in clinical trials to extend the time window for ET and tPA treatment. Interestingly, it was found that hyperconstricted LMAs from spontaneously hypertensive rats were highly unresponsive to dilation by the NO donor sodium nitroprusside [25]. While LMAs from normotensive and aged rats dilated 60-80% of maximum, LMAs from hypertensive rats dilated only ~20%. If there is a human counterpart to these co-morbid hypertensive rats that have LMAs that are relatively unresponsive to NO donors, it suggests a subpopulation of stroke patients will not respond either and this approach may be limited. That some animals and potentially human stroke patients are unresponsive to certain treatments highlights the complexity of stroke conditions and the state of the vasculature prior to and during stroke, including collaterals. A greater understanding of the functional state of the vasculature under multiple conditions and co-morbid states may help to tailor treatments that are effective in a greater number of patients.

Targeting recanalization and reperfusion as a neuroprotective strategy

In the pre-ET era, recanalization therapies were limited by a short time window for which they provided benefit and low rates of reperfusion. Importantly, studies in animals and humans have shown that angiographic recanalization does not necessarily lead to complete reperfusion in downstream tissues [46-51]. Incomplete reperfusion may be a primary factor that increases perfusion deficit, decreases efficacy of early thrombolysis, and limits the ability to deliver neuroprotective agents to areas other than the penumbra [48,52-56]. The importance of early recanalization was shown in the EXTEND-IA trial where effective thrombectomy arrested core expansion. It is currently unclear what factors decrease post-ischemic reperfusion CBF, but has been attributed to capillary disturbances resulting from glial cell swelling [49], clogging of capillaries by microthrombi and immune cells [48,50,57,58] and pericyte-induced reductions in diameter [59]. However, it should be noted

that the large network of capillaries is not the site of greatest resistance to flow in the brain and therefore targeting capillary reductions in flow may not be as beneficial as targeting upstream parenchymal arterioles that are high resistance and the bottleneck to flow to the brain parenchyma [60-62]. In fact, studies have shown that parenchymal arterioles undergo vasoconstriction in response to early post-ischemic reperfusion, a time period important for preventing infarct expansion [63].

Potential targets for vascular protection during reperfusion

An important vascular target during post-ischemic reperfusion may be the hyperconstricted parenchymal arterioles that increase small vessel resistance. Parenchymal arterioles undergo vasoconstriction in response to early post-ischemic reperfusion due to calcium sensitization of the vascular smooth muscle [63]. Parenchymal arterioles are unique vessels in the brain and have greater tone at lower pressures than pial arteries due to a lack of influence of the large-conductance calcium-activated potassium (BK) channel [64]. In addition, similar to LMAs, parenchymal arterioles appear to have basal SK/IK channel activity that counteracts vasoconstriction. Thus, SK/IK channel activation may not only increase perfusion to the penumbra due to an effect on LMAs, but also improve post-ischemic reperfusion by decreasing small vessel resistance. Also similar to LMAs, ROCK inhibition may provide a selective target to decrease small vessel resistance during early reperfusion since its involvement in myogenic tone is through calcium sensitization of smooth muscle, the mechanism by which ischemia and reperfusion are increasing vasoconstriction [41,63].

Post-ischemic reperfusion is also associated with secondary brain injury including edema and hemorrhage that is also time-dependent, i.e., the greater delay in reperfusion causes greater reperfusion injury [10]. While early reperfusion provided by ET inherently limits reperfusion injury due to selection of patients with small core infarctions, good collateral status on imaging, and rapid reperfusion, limiting reperfusion injury is a consideration of if ET is to be extended to more patients. Hemodynamically, there are several considerations for vascular protection with ET that are unique. For example, rapid removal of an occlusion by mechanical means may alter hemodynamics during reperfusion compared to slower more progressive restoration of flow. Depending on the state of the vasculature, rapid reperfusion will produce substantially increased shear stress and hydrostatic pressure on the downstream microcirculation, leading to edema and/or hemorrhage [65,66]. Thus, one potential approach to limiting reperfusion injury is to more gradually increase flow during ET to limit the high hydrostatic pressure that occurs during reperfusion. Other approaches include protection of the blood-brain barrier (BBB) with pharmacologic agents on board prior to clot removal to prevent its disruption. Numerous agents have been investigated to protect the BBB during reperfusion and include protein kinase C inhibition, matrix metalloproteinase inhibition and oxidative stress inhibition [67-69]. However, similar to other vascular targets, the BBB is more prone to disruption under certain co-morbid states. Diabetes causes tremendous edema due to several factors including enhanced protein kinase C activation and higher oxidative stress [68]. Similarly, hypertension is associated with increased vascular endothelial growth (VEGF) and oxidative stress that can increase both hemorrhage and edema [70,71]. Thus, agents on board that inhibit these processes prior to recanalization with ET or IA delivery of these agents during ET (see below) could be effective at preventing reperfusion injury.

IA treatment and ET

IA treatment includes both delivery of compounds directly into the cerebral circulation as well as manipulating blood flow within specific brain regions. There are several advantages to IA drug delivery especially when used in combination with ET. First, IA injection can deliver a highly concentrated agent that restricts the initial volume of distribution to one cerebral hemisphere. Therefore, relatively high arterial concentrations can be achieved in low doses, limiting systemic toxicity [72-74]. Second, IA delivery of drugs seems to have a higher free drug concentration than systemic injection which further concentrates and enhances delivery [75]. Third, IA delivery is rapid and can deliver high concentrations to the brain and vasculature. This may be particularly advantageous in preventing reperfusion injury that occurs within seconds to minutes of initiating reperfusion [76]. Advancements in ET devices make IA delivery and manipulation of CBF feasible, but the practice is limited because of a poor understanding of the advantages and disadvantages of this approach, and a lack of sufficient research and models to advance the potential for IA treatment of acute stroke.

There are several major considerations for IA treatment and delivery of neuroprotective or vascular protective compounds. First, anatomic variation in cerebral arteries, most notably the circle of Willis collaterals, will influence regional distribution of a compound after intra-carotid injection. The extent of collateral communication varies significantly in humans that can influence segmental vascular resistance and hence flow [77-80]. Second, blood flow can change over time and with treatment, affecting the regional concentration of the drug within the brain tissue. For example, nicardipine given for vasospasm will initially be high in concentration at the site of spasm, but decrease in concentration as vasodilation occurs and flow increases. Kinetic modeling of IA drug infusions have been done [72,75,81] but several assumptions need to be made, including uniform mixing of the drug in the blood, steady-state free drug concentrations based on conventional steady-state drug-protein interactions, constant clearance over time, constant regional blood flow, and homogeneous distribution within the arterial and brain compartments [81].

A major issue for neuroprotective treatment (as opposed to vascular protection) of brain tissue with IA delivery is how much drug in plasma is available to cross the blood-brain barrier (BBB) that will restrict proteins >400 Daltons due to the presence of complex tight junctions [82]. Although the BBB properties are present throughout the brain, the electrical resistance of tight junction is less in the larger pial arteries [82,83]. Thus, larger proteins may pass into the brain through pial vessels, but the surface area for distribution is considerably less than the microcirculation. Whether or not the BBB has increased permeability during acute stroke depends on the duration and severity of ischemia and reperfusion and the presence of co-morbidities especially diabetes that is associated with significant microvascular damage [84-86]. In addition, BBB disruption occurs mostly during reperfusion, making IA delivery an attractive approach in combination with ET [87]. However, it cannot be assumed that the BBB will be open for delivery of neuroprotective drugs since this process is not homogeneous.

Brain blood flow is also not homogeneous but varies considerably between gray and white matter [88-90], and is highly affected during ischemia and reperfusion. Baseline variability in CBF can result in differences in drug concentrations after IA injection; however, changes in CBF after IA injection in combination with ET is likely unique and will depend on the response of the various arterial segments to rapid reperfusion. For example, pial arteries and arterioles dilate in response to ischemia and reperfusion whereas parenchymal arterioles constrict, likely changing segmental vascular resistance that will influence blood flow and drug concentration [63,91,92]. In fact, high resting CBF is disadvantageous during IA drug delivery to the brain because it decreases peak drug concentrations due to dilution by the arterial blood, decreases drug transit time and augments efflux from the brain [72]. However, during ischemia and reperfusion, heterogeneous blood flow and BBB permeability make it difficult to determine local concentrations of drug in the brain that will vary depending on composition of the compound (size, charge, polarity, lipophilicity, etc.), and blood flow in the various brain regions of interest. Although complex, the advantages of IA delivery, especially in combination with ET are great: minimizing total dose, decreasing regional and systemic toxicity, directly and rapidly treating affected brain and vasculature, and limiting reperfusion injury. In this ET era, IA delivery of neuroprotective and vascular protective agents should be explored further with appropriate models.

The need for combined therapies and selective stroke treatment

The recent advances in ET seem to have opened a new page in the treatment of acute ischemic stroke. Clearly, in the recent ET trials short time to recanalization, selection of patients with small ischemic core volume and good collateral circulation improve the odds of a good clinical outcome [2,4]. In particular, the remarkable time dependency in revascularization therapy suggests that that any further improvement in devices for ET will not translate in a dramatic improvement in patient outcomes. For example, in a recent analysis of the The North American SOLITAIRE Acute Stroke (NASA) registry, time to recanalization had an estimated 9% increased risk of death within 90 days per 30-minute delay from symptom onset to recanalization [93]. The same estimate of a 9% increased risk per 30-minute delay was reported in a study of poor outcomes or death following successful recanalization [94]. Time dependency of brain ischemia has been extensively reported with IV tPA as well [95,96] that is most likely related to delayed time to recanalization and therefore futile reperfusion [97,98]. However, the process times for the recent ET trials demonstrate that more rapid reperfusion with ET would be difficult to improve upon and therefore combined approaches to improve outcome should be explored.

While rapid recanalization with ET is clearly beneficial to stroke outcome, there are still patients who do poorly. From an endovascular technology stand-point, advancements in devices are already taking place. The aim is first pass recanalization in the highest possible number of patients. In addition, there is a direct correlation between speed of recanalization and number of patients who will achieve a good outcome. Therefore, improvements in system of care will translate in faster times from door to groin puncture and from door to recanalization. However, further improvements in either devices or speed to recanalization, may not translate in a dramatic improvement in the percentage of patients with 90 days mRS ≤2, suggesting additional approaches are necessary. In addition, we need to consider that

there are the small number of patients that are eligible for ET. Considering all these challenges, coupling neuroprotective strategies targeting the collateral circulation and/or the ischemic core to effective and fast recanalization may improve both the number of patients treated and the number of patients that achieve good outcomes.

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