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REVIEW

Evolving Stroke Systems of Care: Stroke Diagnosis and Treatment in the Post-Thrombectomy Era

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Abstract
Thrombectomy became the gold-standard treatment of acute ischemic stroke caused by large-vessel occlusions (LVO) in 2015 after five clinical trials published that year demonstrated significantly improved patient outcomes. In subsequent years, advances in stroke systems of care have centered around improving access to and expanding patient eligibility for thrombectomy. The prehospital and acute stroke treatment settings have had the greatest emphasis. Numerous prehospital stroke scales now provide emergency medical services with focused physical exams to identify LVOs, and many devices to non-invasively detect LVO are undergoing clinical testing. Mobile stroke units deployed throughout Western Europe and the USA also show promising results by bringing elements of acute stroke care directly to the patient. Numerous clinical trials since 2015 have aimed to increase candidates for thrombectomy by expanding indications and the eligibility time window. Further optimizations of thrombectomy treatment have focused on the role of thrombolytics and other adjunctive therapies that may promote neuroprotection and neurorecovery. While many of these approaches require further clinical investigation, the next decade shows significant potential for further advances in stroke care.

Keywords Stroke · Thrombectomy · Neurotherapeutics · Mobile stroke unit · Large-vessel occlusion

Background

In 2015, five landmark randomized controlled trials demonstrated improved outcomes after 90 days in acute ischemic stroke patients treated with mechanical thrombectomy compared with medical therapy, namely MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA (Table 1) [1–5]. The exciting results from these trials were the first major improvement of treatment of acute ischemic stroke since the NINDS trial demonstrated benefit with thrombolytics administered within 3 h of the onset of stroke symptoms [6]. Robust additional evidence has since accumulated to support thrombectomy for acute ischemic stroke. A meta-analysis of the initial five trials found a number needed to treat of 2.6 to decrease a patient's modified Rankin Score by one point, with no demonstrated increase in mortality or intracranial hemorrhage [7].

There has since been increased focus on (1) improving prehospital identification of large-vessel occlusions (LVO); (2) increasing access to endovascular thrombectomy (EVT) by increasing the number and distribution of EVT-capable hospitals, shortening the time to treatment at established sites, as well as improving the system of care to transport patients to the most appropriate hospital as first destination; (3) expanding the eligible population (e.g., large core infarcts) through clinical research; and (4) identifying agents which can delay the progression of ischemia to prolong the window for EVT or that provide other mechanisms of neuroprotection to enhance the benefits of EVT [8–15].

In addition to the increased academic and research focus, the demonstrated clinical benefit of thrombectomy has been recognized by the broader medical community and is now a fundamental component of stroke care.

The American Stroke Association's (AHA/ASA) 2019 *Recommendations for the Establishment of Stroke Systems of Care* described the eight components of a stroke system of care: community education, primordial prevention, primary prevention, EMS response, acute stroke treatment,

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Table 1 Original randomized controlled trials of thrombectomy versus medical therapy

Trial	Author	Number of patients	Gender	Findings
MR CLEAN [1]	Berkhemer et al.	500	292 M/208 F	In this trial in the Netherlands, patients that underwent thrombectomy for LVO had a 13.5% higher rate of functional independence
ESCAPE [5]	Goyal et al.	316	151 M/165 F	In this trial at 22 centers worldwide, patients receiving thrombectomy had a higher rate of functional independence with a common odds ratio of 2.6
REVASCAT [3]	Jovin et al.	206	109 M/97 F	This trial in Catalonia Spain was stopped early due to the publication of other trials that demonstrated benefit. Thrombectomy reduced the severity of disability with an adjusted odds ratio of 1.7 for a one point improvement in modified Rankin score at 90 days
SWIFT PRIME [4]	Saver et al.	196	99 M/95 F	This trial was stopped early due to efficacy. Thrombectomy restored perfusion in 88% of patients and significantly reduced disability
EXTEND IA [2]	Campbell et al.	70	34 M/36 F	This multicenter trial from Australia and New Zealand was stopped early due to efficacy. Thrombectomy improved neurologic function at 3 days and functional outcomes at 90 days

secondary prevention, stroke rehabilitation, and continuous quality improvement [9]. In its discussion of acute stroke treatment, the document states that the demonstrated benefit of rapid thrombectomy warrants the development of stroke systems that identify thrombectomy-eligible patients and enable the timely delivery of this treatment [9]. National guidelines advocate for a two-tier system of disseminated primary stroke centers (PSC) and acute stroke ready hospitals (ASRH) capable of providing thrombolysis and comprehensive stroke centers (CSC) and thrombectomy-capable stroke centers (TSC) capable of providing higher levels of care [16]. Use of optimal system simulation can increase the efficiency of this two-tier setup and enable access to thrombectomy to greater portions of the population within 1 h [17].

Since the introduction of mechanical thrombectomy, EMS and acute stroke treatment, as components of stroke systems of care, have received the most attention. Public education has also aimed to increase awareness of stroke systems to decrease disparities [18, 19]. The Hip-Hop Stroke trial investigated a culturally tailored 3-h class for students in 6th–12th grade and their parents and concluded that it was an effective model for improving stroke preparedness in economically disadvantaged minorities [20]. Other interventions have focused on addressing risk factors for stroke, like diabetes and hypertension, through community health coaching and increasing access to primary care [21].

Research in the prehospital setting has focused on investigating methods to improve the accuracy of recognition and detection of acute stroke by emergency medical services (EMS) using new prehospital stroke scales and the implementation of mobile stroke units to bring treatment to directly to the patient [8, 22–24]. In the acute stroke treatment setting, efforts have focused on investigating the use of thrombolytics as adjuncts to mechanical thrombectomy as well as investigation of novel therapeutic targets such as neuroprotection [12, 14, 25].

In this review, we will discuss advances in the prehospital diagnosis and management of acute ischemic stroke and the optimization of stroke treatment in the setting of mechanical thrombectomy with adjunctive thrombolytics and novel neuroprotective agents.

Emergency Medical Services and the Response to Stroke

For many stroke patients, the first encounter with the healthcare system following the acute onset of symptoms is with EMS. Estimates suggest that 50–60% of patients hospitalized following an acute ischemic stroke arrive to the hospital via EMS [26–28]. Optimizing prehospital stroke care to rapidly identify, triage, and even treat stroke patients in the field has the potential to improve patient outcomes.

Mobile Stroke Units

Arguably, the most exciting advancement in the treatment of stroke in the prehospital setting is the development of mobile stroke units (MSU). These ambulances are equipped with a CT scanner and lab testing capacity, operated by a team trained in the management of acute ischemic stroke, and intended to bring treatment previously reserved for the hospital directly to a stroke patient [29]. The concept of a mobile stroke unit was proposed in 2003 by Fassbender et al. in a letter to the editor of the journal *Stroke* and consists of an ambulance equipped with a CT scanner and testing equipment to allow for thrombolysis administration in the prehospital setting [30].

The impetus for creating these specialized ambulances stemmed from efforts geared at increasing the proportion of thrombolysis-treated patients who receive treatment within the "golden hour" [31]. It is well-established that the faster ischemic stroke patients are treated with thrombolysis, the better the outcomes that will be observed. Indeed, among all patients treated with thrombolysis, those treated within the golden hour are more likely to be discharged home without increasing the risk of mortality or intracranial hemorrhage [32]. In principle, these mobile stroke units would help not only increase the number of people eligible for thrombolysis, but also reduce overall disability due to stroke.

The first mobile stroke unit was started in 2009 at the Saarland University Hospital in Homburg, Germany, and a few years later in 2014, USA's first mobile stroke unit debuted in Houston, Texas. Currently, an estimated 20 cities in the USA have deployed mobile stroke units [31]. In its 2019 recommendations, the AHA/ASA struck an optimistic tone regarding the proliferation of MSUs throughout the USA but urged a cautious approach, stating that evidence to support their use was minimal [9]. Further complicating MSU adoption in the USA is lack of established reimbursement models for the service that these ambulances provide [9].

Evidence to support the use of mobile stroke units to improve patient outcomes is beginning to appear in the literature. To date, at least five controlled trials assessing the efficacy of MSUs have been completed [24, 33–36]. The most recent and largest trials were published in 2021. Ebinger et al. (B_PROUD) and Grotta et al. (BEST-MSU) conducted non-randomized prospective trials comparing MSUs to standard EMS in Germany and the USA, respectively. Both trials included over 1500 patients in their analyses and assessed patient outcomes using a modified Rankin scale at 90 days. Ultimately, patients whose stroke treatment began in an MSU had significantly better outcomes. Further evidence is emerging that mobile stroke units may improve outcomes for all transported ischemic stroke patients, not just those eligible for thrombolytics, while maintaining a high degree of patient safety [36, 37]. The results of these and other trials are summarized in Table 2.

As more evidence supporting the use of mobile stroke units to benefit patient outcomes accumulates, stakeholders, including the community, governments, and leaders, in the field of stroke treatment will need to cooperate to implement these units and develop reimbursement models to make these units sustainable [38]. Health economics evaluations from the B_PROUD and BEST_MSU studies are currently underway and should provide clearer data on the cost-effectiveness of MSUs [38]. Though mobile stroke units are an exciting development in the prehospital treatment of stroke, the related expense without an established reimbursement model and uncertainty about their cost-effectiveness makes further deployment a slow, long-term goal as a component of a stroke system of care.

Prehospital Stroke Detection

The development of prehospital stroke scales that enable EMS to rapidly detect stroke (especially large-vessel occlusion) and appropriately triage patients is a pragmatic and inexpensive way for EMS to help improve patient outcomes. Given the strong evidence supporting the use of thrombectomy for the treatment of LVO strokes, the ability of EMS personnel to detect suspected LVO stroke in the prehospital setting and appropriately triage these patients to thrombectomy-capable hospitals would have a major impact on the public health [39]. The AHA/ASA's Mission: Lifeline algorithm for prehospital stroke triage recommends direct transport to a thrombectomy stroke center or comprehensive stroke center instead of a primary stroke center or acute stroke ready hospital if the transport time is < 30 min [40].

The key to successfully triaging suspected strokes to appropriate levels of care is providing EMS with the

Table 2 Controlled mobile stroke unit trials

Year	Author	Number of patients	Gender	Findings
2012	Walter et al. [33]	100	65 M/35 F	Patients transported via MSU had substantially shorter median times from alarm to therapy decision
2014	Ebinger et al. [34]	523	267 M/267 F	In this large, non-randomized controlled trial, patients treated by an MSU in Berlin were found to have a decreased time to treatment without an increase in adverse events
2019	Helwig et al. [35]	116	44 M/72 F	MSU-based management of patients with acute ischemic stroke enabled 100% accurate triage decisions compared to 70% for patients seen by conventional EMS optimized by LAMS
2021	Ebinger et al. [36]	1543	820 M/723 F	Prospective, non-randomized controlled intervention trial from Berlin. Patients treated using an MSU had significantly lower disability at 3 months
2021	Grotta et al. [24]	1515	773 M/742 F	In patients eligible for tPA, utility-weighted disability outcomes at 90 days were better following treatment by an MSU

resources to detect symptoms suggesting large-vessel occlusions quickly and reliably. Numerous prehospital stroke scales have been developed in the last decade, including the Cincinnati Stroke Triage Assessment Tool (C-STAT); Facial palsy, Arm weakness, Speech changes, Time, Eye deviation, Denial/neglect (FAST-ED) scale; Rapid Arterial Occlusion Evaluation Scale (RACE), Los Angeles Motor Scale (LAMS); and Vision, Aphasia, Neglect (VAN), all of which are mentioned in the 2019 systems of care paper. The paper stopped short of recommending one score over others due to insufficient data on scale performance at that time [9, 40].

The most comprehensive trial of prehospital stroke scale for LVO triage is the PRESTO trial, which compared eight prehospital scales in a prospective observational study [8]. Paramedics were trained to use a mobile app to assess items from the following prehospital stroke scales: LAMS, RACE, G-FAST, C-STAT, PASS, CG-FAST, CPSS, and the FAST-PLUS test [8].

Of 1039 suspected stroke patients identified by paramedics over an approximately 1-year period, 120 had confirmed LVO. All patients with a normal blood sugar, at least one point on the FAST scale, and aged 18 years or older were included in the trial. Paramedics were guided through a nine-item prehospital patient assessment using a mobile app after which the patients were transported to an emergency department, where standard of care was continued. The primary outcome of interest was the diagnosis of ischemic stroke with an LVO as confirmed by neuroradiologists using CT angiography. The RACE scale was found to perform best with an AUC approaching that of the NIHSS (0.83 vs 0.86), as well as high sensitivity and specificity. The AUCs for G-FAST and CG-FAST were also high, at 0.80 for both. The authors suggested that RACE, G-FAST, and CG-FAST may be suitable prehospital stroke triage scales to identify patients with LVOs, though they noted that further studies are necessary to determine the impact on clinical outcomes of stroke patients [8].

A key limitation of the PRESTO study was that its conduct in the Netherlands only, which limits generalizability to more diverse populations with different stroke/prehospital systems [41]. Further, while the RACE scale performed best in the study, there are up to 16 different scores to apply to six items on the scale. Thus, it is not simple to use, and the ability to retain knowledge of use of the scale over time has not been reported [22].

In addition to prehospital stroke scales to identify patients with LVOs, recent studies have investigated the use of non-invasive brain-monitoring devices by EMS [42]. These devices utilize a variety of technological approaches, including accelerometers, electroencephalography (EEG), microwaves, near-infrared, and transcranial Doppler ultrasound to detect LVOs [42]. Though the concept is exciting and shows promise, a systematic review published in 2022 concluded that these technologies require further development [43]. Further, the lack of large, multicenter studies and the heterogeneity of study designs and populations in available literature prevent definitive statements about their clinical utility [43].

Novel Approaches to Optimize Thrombectomy Delivery

The RACECAT trial used the RACE prehospital scale to assess a strategy of transporting patients with high concern of LVO (defined as RACE score between 5 and 9) directly to a thrombectomy-capable facility instead of local stroke centers for initial evaluation and possible treatment with thrombolytics in nonurban Catalonia [44]. Patients were randomized to be transported to the closest local stroke center ($N=713$) followed by a thrombectomy-capable hospital or directly transported to a thrombectomy hospital ($N=688$). The authors assessed disability at 90 days using the modified Rankin scale as the primary outcome. In the final analysis, 920 patients with confirmed acute ischemic stroke were included. The data failed to demonstrate a benefit of bypassing local stroke centers to transport patients directly to thrombectomy-capable hospitals. This contrasts prior conclusions drawn from observational studies advocating for bypassing local stroke centers if there was high suspicion of LVO [45–48]. Further trials are needed to validate these findings.

Another novel idea utilizing EMS to optimize stroke care is the transport of neurointerventionalist teams by helicopter to hospitals where patients with stroke due to large-vessel occlusions have presented, i.e., transporting the neurointerventionalist to the patient instead of transporting patients to another hospital. Much of the motivation for trialing this strategy is an insufficient number of trained neurointerventionalists and difficulties in transporting patients to thrombectomy-capable facilities in a timely manner [49, 50].

Hubert et al. assessed this strategy in a non-randomized controlled intervention study in Germany [51]. On alternating weeks, patients in a nonurban area received thrombectomy treatment either following transfer from a local stroke center to a compressive stroke center or a flying interventional team was sent to the hospital where the patient was located to perform the thrombectomy. The primary outcome of this study was time from the decision to perform a thrombectomy to the start of the procedure. Patients treated by the flying team had a markedly lower median (IQR) time from decision to pursue EVT to groin puncture, 58 (51–71) min compared to 148 (124–177) min [51]. Further studies are necessary to validate these results.

Acute Stroke Treatment

Although developments in the prehospital system of stroke care may improve stroke patient outcomes, the greatest gains to be made ultimately rest with the treatments used for acute stroke. Despite the excitement about the impact of the thrombectomy trials on patient outcomes, only 27% of treated patients are disability free at 90 days, and there is much room for improvement [1–5]. Potential areas for investigation include expanding eligibility for thrombectomy, bypassing thrombolysis, adjunctive intra-arterial medications combined with thrombectomy, and neuroprotection.

Expanding Eligibility for Thrombectomy

One of the limitations of the 2015 thrombectomy trials was a focus exclusively on anterior circulation strokes [7]. The evidence regarding the use of thrombectomy in posterior circulation strokes is sparse. Two randomized clinical trials have been conducted to investigate the use of thrombectomy in posterior circulation strokes [52]. The Basilar Artery Occlusion Endovascular Intervention vs Standard Medical Treatment (BEST) attempted to conduct a randomized trial of thrombectomy for patients with vertebrobasilar occlusion within 8 h of symptom onset [53]. The study's primary outcome was a modified Rankin scale score of 3 or lower at 90 days. Unfortunately, the BEST trial was terminated early due to high crossover rates between the control and treatment groups, and intention to treat analysis of the primary endpoint did not show any difference in favorable neurologic outcomes [53].

A second trial was published in 2021. The Basilar Artery International Cooperation Study (BASICS) conducted a "multicenter, open-label, international, randomized, controlled trial with blinded outcome assessment" of 300 patients presenting with basilar artery occlusion within 6 h of onset of stroke [54]. Like the BEST trial, the primary outcome was a favorable neurologic outcome, defined as an mRS score of less than three. No difference in outcome was found between the control and intervention groups. However, the analysis revealed wide confidence intervals on the calculated common odds and risk ratios [54]. Larger studies with higher statistical power are necessary to determine whether thrombectomy is beneficial in this patient population. Unfortunately, addressing this clinical question has been hampered by difficult patient recruitment and study implementation [54].

In 2018, two randomized, controlled trials investigated the efficacy of thrombectomy in patients presenting with acute ischemic stroke between 6 and 16 h (DEFUSE-3 trial) and 6 and 24 h (DAWN trial) following symptom onset. Trial eligibility depended on the size of the infarct "core" or dead brain tissue relative to the "penumbra" or salvageable brain tissue. Thrombectomy-treated patients had better outcomes compared to control. Both the DAWN and DEFUSE-3 trials provide strong evidence for the use of thrombectomy past 6 h following the onset of stroke symptoms [10, 11, 52]. However, it has since been learned that CT perfusion may overestimate "core" size, and it is possible that patients who may benefit from thrombectomy are excluded from treatment by DAWN/DEFUSE-3 criteria.

Ongoing trials are evaluating the impact of thrombectomy on "large core" strokes, with some of these trials beginning to be published [55–57]. The SELECT2 and ANGEL-ASPECT trials investigated the efficacy of EVT on patients with ischemic strokes and large infarct cores [58, 59]. The SELECT2 trial took place in the USA, Canada, Europe, Australia, and New Zealand, while the ANGEL-ASPECT trial took place in China. Both trials were prospective, multicenter, randomized, open label studies that compared EVT with standard medical care to standard medical care alone in patients with occlusions of the first segment of the middle cerebral artery or the distal internal carotid artery. The studies were stopped early for efficacy. Patients receiving thrombectomy had markedly improved outcomes at 90 days on the modified Rankin scale (OR 1.51, 95% CI 1.20–1.89, and 1.37, 95% CI 1.11–1.69, for the SELECT2 and ANGEL-ASPECT trials, respectively) [58, 59].

Is Thrombolysis Necessary in Patients Going to Thrombectomy?

After 20 years as the only treatment option in acute ischemic stroke, thrombolysis and its necessity have been questioned in patients in whom thrombectomy is planned. Numerous studies investigating the need for thrombolysis in ischemic stroke patients going to thrombectomy have been published (Table 3). Available evidence suggests that thrombolysis remains warranted in eligible patients even if ultimately undergoing thrombectomy [12–15].

The DIRECT-MT trial randomized 656 Chinese patients with a large-vessel occlusion to receive either mechanical thrombectomy alone (327 patients) or a combination of thrombolytics with mechanical thrombectomy (329 patients). Thrombectomy alone was found to be noninferior to thrombectomy plus thrombolytics. However, the margin used to declare noninferiority was felt to be generous and thus inadequate for recommending skipping thrombolysis in eligible patients [13, 60].

The DEVT trial was another Chinese trial of 234 patients randomized to thrombectomy alone versus thrombolysis plus thrombectomy. Sixty-three out of 116 patients (54.3%) in the thrombectomy-alone group achieved functional independence compared with 55 out of 118 patients (46.6%) in

Table 3 Trials of thrombectomy with and without thrombolytics

Trial	Author	Number of patients	Gender	Findings
DIRECT-MT [13]	Yang et al.	656	370 M/286 F	This trial found noninferiority of thrombectomy alone in acute ischemic stroke patients
DEVT [12]	Zi et al.	234	114 M/120 F	Second trial from China that also demonstrated noninferiority of thrombectomy alone with respect to functional outcomes
SKIP [14]	Suzuki et al.	204	128 M/76 F	This Japanese trial failed to demonstrate noninferiority of thrombectomy without thrombolytics
MR CLEAN-NO IV [15]	LeCouffe et al.	539	305 M/234 F	This multicenter European trial failed to demonstrate noninferiority of thrombectomy without thrombolytics

the combination-treatment group. The lower bound of the confidence interval was greater than the prespecified noninferiority margin of − 10% [12]. Again, the noninferiority margin in this trial was generous.

The SKIP trial was a Japanese trial of 204 patients with large-vessel occlusions. A favorable outcome (mRS at 90 days) occurred in 60 out of 101 (59.4%) patients in the thrombectomy-alone group and 59 out of 103 (57.3%) patients in the combination-treatment group. The trial failed to demonstrate noninferiority of thrombectomy alone [14]. Finally, the MR CLEAN-NO IV trial [15] randomized 539 European patients to thrombectomy-alone versus thrombectomy-plus thrombolysis. This trial also failed to demonstrate noninferiority of thrombectomy alone [15]. Two other trials investigating this clinical question are ongoing—the SWIFT DIRECT and DIRECT-SAFE trials [14].

Adjunctive Intra-arterial Medications and Thrombectomy

Another clinical question being investigated is whether thrombolytics administered *after* thrombectomy are beneficial in stroke patients with large-vessel occlusions [61]. The impetus for this clinical question is the observation that only 27% of people treated with thrombectomy were disability free at 90 days, despite 71% of patients achieving adequate reperfusion [7]. This “no reflow” phenomenon may be due to lack of reperfusion of the microvasculature distal to the site of the thrombus, despite large arterial recanalization [61, 62]. The CHOICE trial was a randomized, double-blind, placebo-controlled multicenter study investigating whether thrombolytics after thrombectomy improve functional outcomes [61].

The initial study design called for enrollment of 100 patients per treatment group to achieve 80% power to detect a difference in the primary outcome (mRS). Unfortunately, due to a combination of factors, including difficulty obtaining the control treatment and the COVID-19 pandemic, the trial was stopped early. The treatment alteplase group had a favorable outcome in 36 out of 61 (59%) patients, compared to 21 out of 52 patients (40.4%) receiving the control treatment (18.4% adjusted risk difference; 95% CI of 0.3–36.4%; $P = 0.47$). Though these results are promising, the small sample size and wide confidence intervals suggest that additional studies are warranted [61].

Novel Neuroprotective and Therapeutic Approaches

Following a series of failed neuroprotective strategies, including glutamate antagonists to attempt decreasing excitotoxicity, anti-inflammatory monoclonal antibodies, ion channel blockers, and free radical scavengers, the last two decades of acute ischemic stroke treatment have focused on restoring perfusion to ischemic brain tissue through the removal of the occluding thrombus [63, 64]. Numerous reasons have been cited for the failure of translating promising preclinical results of neuroprotective agents into novel clinical therapies including selection and assessment bias in the preclinical space and under-powered studies in the clinical realm [65].

The development of EVT and a better understanding of the importance of recanalization, new guidelines increasing the rigor of preclinical study designs, and therapeutic approaches targeting multiple pathways in the setting of ischemic injury are driving the development of several new neuroprotective candidate therapies [65].

In 2020, the first large multicenter randomized controlled trial of nerinetide, an eicosapeptide that showed promise as a neuroprotectant in animal models through the inhibition of post-synaptic density protein 95 (PSD-95), was published [25]. PSD-95 interacts with NMDA receptors and results in excitotoxicity through the activation of neuronal nitric oxide synthase [66]. Following this discovery, researchers set out to create drugs that perturb this harmful interaction through the development of eicosapeptides that disrupt the coupling of PSD-95 and NMDA receptors in ischemic brain tissue [67]. Fusing the domain of PSD-95 that binds to the NDMA receptor with the Tat protein of HIV-1 led to the creation of a peptide that successfully transduces the neuronal cell membrane and reduces previously described neurotoxicity [67].

After promising results in primates and a Phase 2 trial in humans undergoing endovascular aneurysm repair, the ESCAPE-NA1 trial sought to establish whether there was a clinical benefit of administering nerinetide to stroke patients [68, 69]. In this phase 3 trial, patients receiving nerinetide did not show improved clinical outcomes at 90 days after stroke. However, subgroup analyses suggested that non-thrombolytic patients may benefit from nerinetide, with a possible explanation being that concurrent administration of alteplase and nerinetide may lead to cleavage of nerinetide and nullify any therapeutic benefit [69]. Further investigation is needed to determine which patient populations may benefit from nerinetide or if the development of new thrombolytics may avoid this interaction.

Other therapies have also shown promise in clinical trials [65]. These therapies include uric acid, a potent antioxidant, which was noted in a recent clinical trial to markedly improve outcomes in patients receiving alteplase (39% compared to 33% of patients having excellent outcomes) [70]. Activated protein C, a protease with anticoagulant activity, was trialed in the RHAPSODY trial and found to be associated with lower rates of hemorrhage and more favorable outcomes; a larger trial to assess its efficacy is in the start-up stage [71].

Looking to the future of neurotherapeutic research, stem cell therapies are a source of enthusiasm and have demonstrated promising results in animal models [72]. Several candidate stem cell sources, including neural, bone marrow, and umbilical cord stem cells, are currently being investigated. Multiple clinical trials are underway, and they may pave the path for the next great advancement in the treatment of acute ischemic stroke.

Conclusion

In the years since the development of thrombectomy as a proven treatment for acute ischemic stroke caused by large-vessel occlusions, the field of stroke care continues to advance to improve the quality of care and the functional outcomes of stroke patients. Acute stroke care is no longer isolated to the hospital setting, but is now composed of a comprehensive system encompassing EMS, hospitals, and rehabilitation centers to optimize the treatment and outcomes of stroke patients [9].

Emerging major advances in this system of care during the "post-thrombectomy era" include improved identification of large-vessel occlusions in the prehospital environment by EMS to facilitate triage of stroke patients to the most appropriate hospital, mobile stroke units that bring treatments to the patient, expansion of candidate patients for thrombectomy, and optimization of reperfusion through adjunctive therapies. The next decade promises to be an exciting time for further reducing societal burden from disability due to stroke.

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Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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