

# Before the Angiography Suite

Prehospital stroke identification, routing, and treatment.

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There have been major advances in the prehospital evaluation and treatment of stroke in the last few decades that have directly affected endovascular care. The main areas of success have been in public education regarding the importance of activating emergency medical services (EMS) when stroke is suspected, prehospital identification of stroke, supportive care in the ambulance, and the routing of stroke patients to designated acute stroke centers. Areas of active investigation include the initiation of neuroprotective agents, use of dedicated mobile stroke unit (MSU) ambulances, and multitiered routing protocols. The eventual goal of prehospital care is to deliver stroke patients in an expedited and effective manner to the closest and most appropriate hospital.

Prehospital care must be responsive to recent developments in endovascular care of ischemic stroke patients with a large vessel occlusion (LVO). The publication of several landmark randomized studies, demonstrating the benefits of combining endovascular thrombectomy in combination with standard stroke care,<sup>1-4</sup> has challenged the prehospital systems of care to reevaluate identification, routing, and treatment protocols. This article reviews the current state of prehospital care of stroke patients; elucidates the most relevant challenges facing the field of prehospital stroke care including neuroprotection, MSUs, prehospital recognition/triage of LVOs, and reviewing ongoing research studies/projects; and looks to the future.

## CURRENT STATE OF PREHOSPITAL STROKE EVALUATION

Currently, 35% to 70% of stroke patients arrive at the emergency department by ambulance, depending on the region. Thus, EMS providers are in a unique position, as they are often the first medical professionals to have contact with a stroke patient. Recognition of

a potential stroke patient begins with EMS dispatch operators who field emergency calls (via 911 in the United States).<sup>5</sup> The sensitivity of dispatcher identification of possible stroke is low, although specificity is high. This is because not all callers are able to correctly identify signs and symptoms of stroke and relay them on the phone. Dispatcher identification of potential stroke leads to the activation of an appropriate EMS team, usually via an advanced life support ambulance.

Most paramedics and emergency medical technicians are trained in the use of validated prehospital stroke recognition tools. The most commonly used instruments include the Face Arm Speech Test (FAST)/Cincinnati Prehospital Stroke Scale (CPSS), the Los Angeles Prehospital Stroke Screen (LAPSS), Recognition of Stroke in the Emergency Room, Melbourne Ambulance Stroke Scale, Ontario Prehospital Stroke Screening tool, and Medic Prehospital Assessment for Code Stroke. FAST/CPSS has three components (unilateral facial weakness, unilateral arm weakness, speech abnormality) and has the highest level of sensitivity, with more complex instruments such as LAPSS reporting higher specificity at the cost of lower detection rates.<sup>6</sup>

Prehospital stroke identification instruments are a key component of prehospital stroke triage protocols, which incorporate last-known well time, transport times, and various other factors. Routing protocols widely vary in characteristics including activation by symptom onset time and destination facility features, reflecting an attempt to match prehospital stroke systems to local geographic resources.<sup>7</sup>

Triage/routing of potential stroke patients to a designated hospital rather than the closest hospital has expanded extensively over the past decade to include the majority of Americans.<sup>8,9</sup> In fact, this expansion of regionalized systemic EMS care dramatically increased the proportion of patients with acute stroke cared for

TABLE 1. COMPLETED AND ONGOING CLINICAL TRIALS OF PREHOSPITAL NEUROPROTECTION

Trial Name	Intervention	Strategy	Design	No. of Patients	Publication Date/ Status
FAST-MAG Pilot	Magnesium	NP	Nonrandomized, historical controls	20	2004
Helsinki EMS	IV and SQ insulin	Homeostasis	Randomized, open/historical controls	23	2011
Aarhus University	Remote preconditioning	NP	Randomized, open label	443	2014
RIGHT	Glyceryl trinitrate	BP, NP	Randomized, open label	41	2014
PIL-FAST	Lisinopril	BP	Randomized, open label	14	2014
FAST-MAG Pivotal	Magnesium	NP	Randomized, blinded placebo	1,700	2015
RIGHT 2	Glyceryl trinitrate	BP, NP	Randomized, open label	850	Recruiting
FRONTIER	NA-1	NP	Randomized, blinded placebo	600	Recruiting

Abbreviations: BP, blood pressure reduction; NP, neuroprotection; SQ, subcutaneous.

at designated primary stroke centers in Los Angeles, California, from one in 10 to more than nine in 10, with no clinically significant increase in prehospital care times.<sup>10</sup> This expansion of EMS systems of care has been in parallel to increases in hospital stroke center certification.<sup>11</sup> Approximately one in three acute care hospitals are currently certified in some manner as a stroke center.<sup>12</sup>

Once a potential stroke patient is identified in the field, there is agreement on the importance of rapid transport, which minimizes delay. Paramedics gather information key to stroke evaluation including last-known well time and current medications per routine before transport. Vital signs are monitored during transport, and the receiving hospital is prenotified in most cases. These steps are outlined in the American Heart Association/American Stroke Association policies to guide systems of stroke care delivery.<sup>13</sup>

Upon arrival to the emergency department, stroke patients are often taken directly to the scanner to minimize delays in evaluation for candidacy for intravenous (IV) thrombolysis. Unfortunately, the majority of neuroimaging for stroke patients presenting in the first few hours after onset is noncontrast CT, although there has been increasing utilization of CTA and perfusion.<sup>14</sup> Development of prehospital imaging in the MSU will be discussed in the following sections.

## CHALLENGES FACING PREHOSPITAL STROKE CARE

### Treatment in the Ambulance

Every minute during a typical large vessel ischemic stroke, up to 1.9 million neurons are lost.<sup>15</sup> The concept that time is brain and that earlier treatment is better has been well established for patients receiving IV thrombolysis as well as endovascular thrombectomy. There are two ways to preserve neurons in acute ischemic stroke (AIS): earlier revascularization or neuroprotection. Neuroprotection has a long history of promising preclinical data but a lack of any clear clinical efficacy. Although the reasons for neuroprotective failure have been well described, it is an approach that still holds promise.<sup>16</sup> The prehospital phase of stroke care aims to reduce delays and save time by rapid triage to appropriate hospitals and can also serve as a period in which to initiate neuroprotective therapy.

There have been multiple clinical trials of prehospital stroke therapy completed, including one phase 3 study of IV magnesium. There are currently two active clinical trials that are enrolling (Table 1). Although it failed to show efficacy, the National Institutes of Health funded the Field Administration of Stroke Therapy Magnesium (FAST-MAG) clinical trial showed that neuroprotective therapy can be started as early as 45 minutes after stroke symptom onset.<sup>17</sup> Of note, subjects enrolled

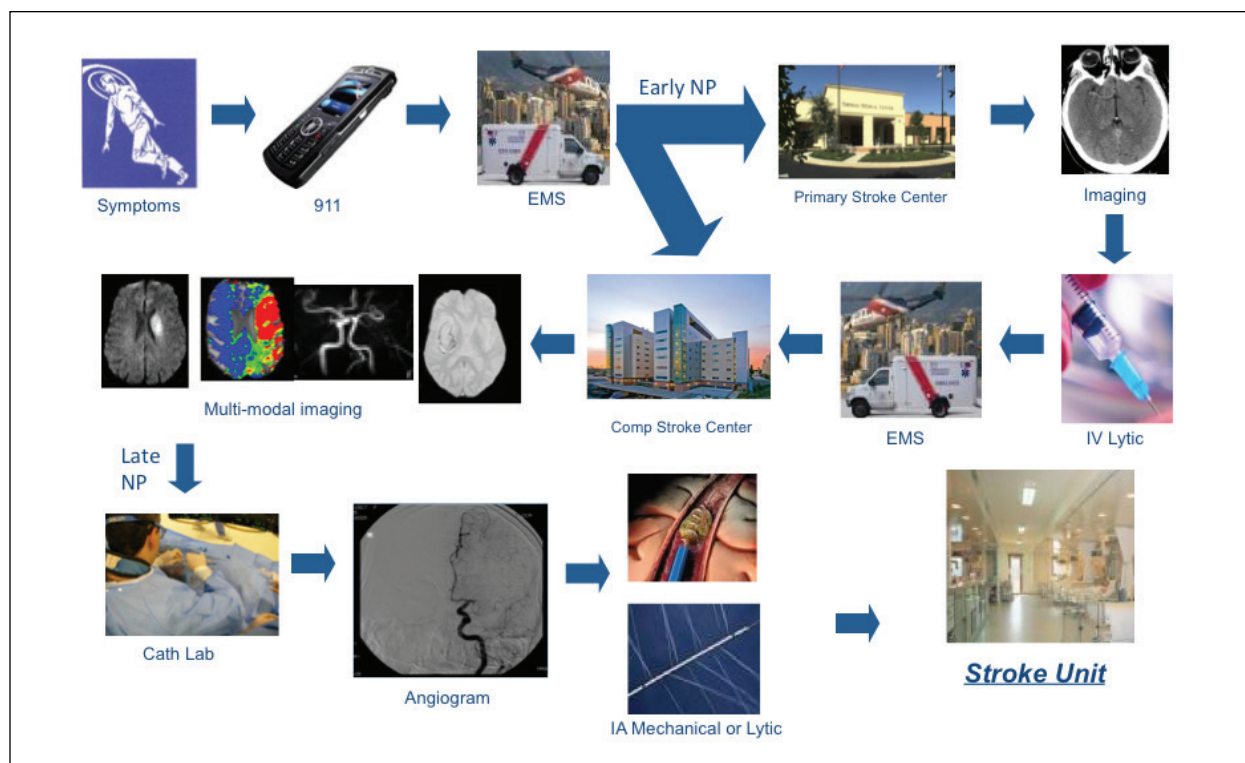


Figure 1. Emerging model of prehospital and emergency stroke care.

in FAST-MAG had exposure to the study agent (IV magnesium sulfate or placebo) for 92 minutes before receiving the IV tissue plasminogen activator (tPA) bolus and for 230 minutes before the start of endovascular therapy (unpublished data). Prehospital neuroprotection combined with endovascular thrombectomy is an exciting potential area of clinical research.

IV thrombolysis in the MSU is another exciting area of prehospital stroke research. MSUs have the potential to reduce the time from when the paramedic arrives on the scene to IV thrombolysis administration. Another potential benefit of MSU care is the ability to perform vessel imaging with CTA to identify LVOs.<sup>18</sup> MSUs are now active in multiple regions in the United States and worldwide. Although MSU care was found to result in a modest 9-minute earlier treatment bolus with IV tPA, the greatest benefits may be in the identification followed by routing of patients to comprehensive stroke centers and endovascular team activation from the field.

#### Identifying and Routing LVO Patients in the Field

Consistent with the paradigm that time is brain, reducing the time from symptom onset to recanalization is vital to improving thrombectomy outcomes. Current systems of prehospital care are centered on the identification of stroke with validated tools such

as the LAPSS. Clinical tools to help identify LVO in the field have been proposed and tested including the Los Angeles Motor Scale,<sup>19</sup> Prehospital Acute Stroke Severity scale,<sup>20</sup> Cincinnati Prehospital Stroke Severity scale,<sup>21</sup> and the Rapid Arterial Occlusion Evaluation scale.<sup>22</sup> These scales are designed to be brief and easy to administer by paramedics, but no single scale has emerged as a consensus leader. Identifying LVOs in the field helps route patients away from a nonendovascular stroke center (often a primary stroke center) to an endovascular-capable center (usually a comprehensive stroke center). The role of two-tiered routing and comparison of this method to the single-tiered method are unknown at this time.

There are three possible methods to approach IV tPA-eligible stroke patients evaluated by EMS in the field:

1. Drip and ship: Transport the patient to the closest stroke center for earlier IV thrombolysis and in-hospital screening for LVO followed by secondary ambulance transport to an endovascular center as indicated.
2. Mothership: Transport the patient directly to the endovascular center in cases where prehospital LVO screen is positive, bypassing closer stroke centers and leading to potentially slower IV thrombolysis but faster endovascular thrombectomy.

3. MSU trip: IV tPA is administered in the MSU, a CTA or clinical scale indicates LVO, then transport the patient to an endovascular center during tPA infusion.

Each of these approaches is likely to have differential benefits and burdens based on region. An important consideration is paramedic/EMS personnel being tied up in longer transports to unfamiliar parts of town. Relationships between primary stroke centers and comprehensive stroke centers are vital to any of the listed processes. The costs of maintaining MSUs are high, and it is difficult to optimize responses to LVO cases. Identifying LVOs in the field can potentially improve stroke care by reducing time to recanalization, but none of the proposed scales are likely to have a particularly high sensitivity or specificity, and overtriage of non-LVO stroke cases to comprehensive stroke centers is a concern.

### THE FUTURE OF PREHOSPITAL STROKE CARE

Important advances in AIS therapy have been achieved, including demonstrated benefits from pre-hospital systems of care,<sup>23</sup> care delivered in MSUs,<sup>24</sup> reperfusion therapy with IV tPA,<sup>25</sup> and from reperfusion

therapy with endovascular thrombectomy<sup>1</sup>; however, current therapies for AIS have limitations.

IV tPA can only be administered after neuroimaging has ruled out intracerebral hemorrhage,<sup>26-28</sup> and although the benefits are strongly time dependent in current clinical practice in the United States, IV tPA is not started until an average of 2 hours and 20 minutes from onset, well after substantial irreversible injury has occurred in most patients.<sup>29</sup> Endovascular therapy is indicated in only 3% to 10% of AIS patients, and patients have to be transported to a tertiary neuroendovascular center. Although the benefit of endovascular therapy is strongly time dependent,<sup>30,31</sup> reperfusion is not achieved until a median of 4 hours and 45 minutes from onset.<sup>1</sup> Because substantial brain injury occurs before reperfusion can be achieved, even among AIS patients treated with endovascular therapy, 73% of patients have an outcome of disability or death.<sup>1</sup>

There are two areas of potential improvement to acute stroke care that can be facilitated in the prehospital phase of care. First, improvements in systems of care that deliver appropriate patients to endovascular-capable hospitals are needed (Figure 1). Second, new,

effective, widely applicable treatments for AIS that can be given at the earliest time periods to preserve as many neurons as possible are needed.

An ideal stroke system of care would be able to reliably identify the presence of LVOs among patients evaluated in the field and urgently route them to the most appropriate facility. Regional cooperation would maximize resources by concentrating endovascular care in the most geographically appropriate locations. This system of care would include nonendovascular primary stroke centers for rapid tPA administration, endovascular primary stroke centers for rapid endovascular treatment without the ability to manage the most complicated cases, as well as comprehensive stroke centers providing 24/7 care for the most complex cases. Centralization of the triage process in the local EMS agency and cooperation and data sharing among all stakeholders are also necessary.

An ideal new treatment for AIS would complement existing reperfusion therapies by having neuroprotective, vasoprotective, and/or collateral-enhancing effects and would be easily administered in the ambulance before brain imaging and soon after onset. It would be inexpensive, readily available, easy to administer, have no major adverse side effects, and have shown safety in hemorrhagic stroke.

## CONCLUSION

The future of prehospital stroke care is bright and full of possibilities. There is a lot that happens to stroke patients before their arrival in the angiography suite. It is only through coordination between emergency medical providers, stroke systems of care, neurologists, radiologists, and neurosurgeons that we can maximize the potential of prehospital stroke care and prime patients for excellent endovascular outcomes. ■

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