Progress Review

The 2012 Feinberg Lecture
Treatment Swift and Treatment Sure

Jeffrey L. Saver, MD

We stand poised on the threshold of a new era in care for acute ischemic stroke, in which treatments will be swift, starting in the first 60 minutes after onset, the golden hour when almost the entire threatened brain region is still salvageable, and treatments will be sure, reopening occluded arteries in almost all patients who will benefit from reperfusion. This narrative review surveys translational clinical research in prehospital neuroprotection and highly effective endovascular recanalization therapy that has helped lay the foundation for this imminent transformation.

I have the honor of delivering the Feinberg Lecture in 2012, a moment of tremendous accomplishment in cerebrovascular disease care. We are preventing and treating acute stroke better than ever before. In the United States, over the past 50 years, the per capita incidence of stroke mortality has decreased by 75%, an immense public health achievement.1 Stroke recently declined from the third to the fourth leading cause of death among Americans. Stroke-prevention trialists find it increasingly difficult to demonstrate benefits of technologically remarkable new treatments because our evolving standard prevention care (past trials translated into practice) has already reduced recurrent vascular event rates to extraordinarily low levels.2

And yet, ours is also a time of increasing peril from cerebrovascular disease. Stroke continues to be a leading cause of disability, death, and dementia worldwide. Moreover, with the aging of the US populace, projections forecast that increasing numbers of acute stroke patients will present to our hospitals every year throughout the next 2 decades.3

As a consequence, the theme of this Feinberg lecture is especially urgent: improving acute ischemic stroke therapy. While our treatments for acute stroke have improved over time, they remain much less effective than our prevention therapies. We have only a small set of proven interventions: intravenous tissue plasminogen activator (IV TPA) recanalization therapy for eligible patients within 3 to 4.5 hours of onset, aspirin to deter clot propagation for the remainder, and supportive care in a Stroke Unit/Stroke Center for all. These treatments fail to assure good outcomes for all too many patients.

The first 15 years of the recanalization era in acute ischemic stroke care, from 1995 to 2010, were filled with drama: a disruptive medical advance, intravenous (IV) fibrinolysis, transformed hospital, regional and national systems of care, fostered new medical subspecialties, and improved patient outcomes worldwide. New devices for endovascular recanalization were innovated in increasingly rapid development cycles. Stroke clinicians spent their practice days responding emergently to code stroke calls; pushing gurneys down hallways; and racing through patient evaluation, scan interpretation, and treatment decision making.

But the excitement of finally being able to help some patients through reperfusion intervention has obscured the substantial limitations that remain. Both IV TPA and first-generation endovascular devices are given too late for maximal benefit and fail to recanalize the target artery too often. We have treatments that are slow and uncertain; we need treatments that are swift and sure. Fortunately, they are near at hand.

Treatment Swift: Prehospital Neuroprotection

The target of therapy in acute ischemic stroke is the ischemic penumbra—the threatened but still salvageable tissue surrounding the infarct core. Unfortunately, the ischemic penumbra is an evanescent phenomenon, lasting only for tens of minutes or a few hours in human patients. In the typical middle cerebral artery ischemic stroke, every minute that goes by without reperfusion, 2 million neurons and 14 billion synapses are irretrievably lost.4 The time window for effective treatment is all too brief. The strict time dependence of therapy benefit is evident from pooled analysis of trials of the one acute therapy that is unequivocally beneficial for human stroke, IV TPA.5,6 The benefit is greatest when the patient receives IV TPA in the 60- to 90-minute window; every 90-minute delay thereafter, the benefit is halved. But, we typically treat patients with tissue plasminogen activator (TPA) in actual practice more than 2.25 hours after onset, when the benefit is only quite modest (Figure 1).7–9

We need to treat patients much sooner after onset. However, we cannot treat much more quickly with TPA or other fibrinolytics. Fibrinolytic agents require brain imaging for safe administration, to unequivocally rule out hemorrhage. Brain imaging takes time. The patient must be transported from the field to the scanner (or the scanner transported to the patient)10 with resultant delay.

Neuroprotective agents offer a potential solution. Neuroprotective treatments interrupt the molecular elaboration of cellular injury in ischemic environments; they do not attack thrombi. They are generally safe, and often potentially beneficial, in hemorrhagic stroke as well as ischemic stroke and could be given before brain imaging.

DOI: 10.1161/STROKEAHA.112.671354

Received July 17, 2012; accepted August 09, 2012.
From the Stroke Center and Department of Neurology, David Geffen School of Medicine, University of California, California, LA (J.L.S.).
Correspondence to Jeffrey L. Saver, MD, UCLA Stroke Center, 710 Westwood Plaza, Los Angeles, CA 90095. E-mail jsaver@ucla.edu
(Stroke. 2013;44:270-277.)
© 2012 American Heart Association, Inc.
Stroke is available at http://stroke.ahajournals.org
Notoriously, however, neuroprotective agents have failed again and again in human stroke clinical trials. In an analysis of all the acute ischemic stroke trials performed in the twentieth century, we found that 49 neuroprotective agents had emerged from preclinical stroke studies having demonstrated substantial promise and entered human testing. These compounds were investigated in 114 clinical trials, enrolling over 21,000 patients. Every agent failed.11 This remarkable record of disappointment is virtually unrivaled in translational science. In the course of 4 decades of research, we became expert at treating rodents with stroke with neuroprotective therapy; humans, not so much. The result was a true Kuhnian scientific crisis in our field. Around the turn of the millennium, many investigators published cri du coeurs identifying fundamental defects in the then regnant design paradigms of preclinical stroke models and translational clinical trials.12–14

Among the several deficiencies identified in neuroprotective clinical trial design, the most important, in my view, is that patients were being treated too late. Most acute ischemic patients in the twentieth century neuroprotection trials were enrolled more than 4 and up to 48 hours after stroke onset, long after what we now know is the optimal, or even any, therapeutic window. Even more recently, from 2000 to 2005, late enrollment was still the rule. Among over 5300 patients in 6 large neuroprotective trials with detailed data, 92% were enrolled beyond 3 hours, only 6% between 2 and 3 hours, and only 1% between 1 and 2 hours. Most striking of all, only 0.2% of patients were enrolled in neuroprotective trials in the first 60 minutes after onset (Figure 2).15 The golden hour, when there is the most brain to save and when agents work best in preclinical studies, has remained a completely unexplored time window in neuroprotective acute ischemic stroke clinical trials.

In order to reach patients faster, our research group turned to the Emergency Medical System (EMS): to ambulances, paramedics, and prehospital care. Our efforts reflect larger trends in acute neurotherapeutics. For status epilepticus, global ischemia after cardiac arrest, traumatic brain injury, and focal stroke, trials and treatments are increasingly shifting to the prehospital setting, responding to the inexorable logic that time lost is brain lost in neurological emergencies. The EMS is the first point of contact for half of all acute stroke patients in the United States, and an even greater proportion of the more severe stroke patients whom we most wish to benefit. As the first medical professionals to encounter severe acute stroke patients, paramedic first responders are uniquely positioned to accelerate the start of cerebroprotective treatment.

As the first neuroprotective agent for focal stroke to test in the prehospital setting, we selected magnesium sulfate, for several reasons. Magnesium sulfate is reliably cerebroprotective in diverse animal stroke models, exerting both vasodilatory and direct neuroprotective and glioprotective effects.16,17 In human clinical trials, magnesium has shown signals of potential neuroprotective efficacy if administered early, including when given before ischemia onset among patients undergoing cardiac bypass surgery and carotid endarterectomy,18,19 shortly after start of global ischemia in patients resuscitated from cardiac arrest,20 and within the first 3 hours of onset in focal ischemic stroke.21 Moreover, magnesium has a well-established safety profile, having been used in clinical medicine for neural emergencies in pregnant women (preeclampsia and eclampsia) for over 75 years. Accordingly, we launched the
Field Administration of Stroke Therapy—Magnesium (FAST-MAG) trial program.

The prehospital setting poses several distinctive challenges of clinical trial design and performance above and beyond those encountered in standard, emergency department (ED) setting trials, including accurate identification of stroke patients, rating of pretreatment stroke severity, elicitation of informed consent in the field before hospital arrival, and randomization to appropriate treatment arm. We developed several methods to address these obstacles in the FAST-MAG program:

- **Stroke identification**—Los Angeles Prehospital Stroke Screen (LAPSS): Paramedics identify stroke patients using the LAPSS, an 8-item diagnostic inventory that takes 1 to 2 minutes to perform, is well validated, and is a standard part of ambulance personnel training worldwide.

- **Stroke severity rating**—Los Angeles Motor Scale (LAMS): The LAMS is a 0 to 5 point rating of motor deficit severity that is derived directly from the face, arm, and grip weakness examination section of the LAPSS. When performing the LAPSS, paramedics also automatically perform the LAMS. Though simple and rapid, the LAMS is a useful assessment of stroke deficit severity, correlating well with concurrently measured 13-item National Institutes of Health (NIH) Stroke Scale (NIHSS) scores, and predicting final 3-month disability, activity of daily living, and neurological deficit outcomes nearly as well as the full NIHSS.

- **Informed consent elicitation**—Cellular Telemedicine: Most recent prehospital treatment trials have been conducted for conditions that render patients incompetent to provide consent, such as cardiac arrest, under regulations permitting waiver of explicit consent in emergency circumstances. In acute stroke, however, many patients retain decision-making capacity, so subject autonomy will be maximized by a process to obtain explicit informed consent in the field. However, it is important that the consent process does not distract paramedics from their time-urgent demands and optimally enable consent provider discussion with physician-investigators who are expert in the study and the cerebrovascular disease process. In the cellular telemedicine enrollment system developed for FAST-MAG, each ambulance carries English and Spanish consent forms for the 4 to 5 hospitals to which it travels most frequently. When paramedics identify a potential study patient who is competent or who is accompanied by a legally authorized representative, the medic hands the consent provider the appropriate consent form and calls an English or Spanish enrolling line. The voice-over-internet-phone enrolling line simultaneously rings trial-dedicated cell phones of 4 available physician-investigators. The first physician-investigator to answer is connected to the ambulance, speaks to patient or the family member in parallel to paramedic delivery of on-site care, and elicits the consent in the field.

- **Drug kit assignment**—Pre-encounter randomization: Prehospital research must adhere whenever possible to the KISS (Keep It Simple … and Straightforward) principle. In the potentially chaotic prehospital setting, complex randomization schemes and multiple drug source bins have a high risk of leading to misallocation. Accordingly, for kit assignment in FAST-MAG, we devised a “pre-encounter randomization” system. Each ambulance is stocked with only a single kit at any one time—the next kit in that ambulance’s permuted block randomization sequence. Each kit contains both the field loading dose and the hospital maintenance dose in a single, shrink-wrapped package, ensuring correct and uninterrupted administration of the study drug through the prehospital-to-hospital handoff. When a patient is enrolled, paramedics use the single kit in the vehicle. Within the next 24 hours, study coordinators restock the vehicle with the next kit in the vehicle-specific randomization sequence.

We initially developed, and demonstrated the feasibility of, this approach in a 20-patient pilot study, the FAST-MAG pilot trial. In the pilot, the time interval from paramedic arrival on scene to start of study agent was substantially less with field than with ED administration, 23 versus 141 minutes (P<0.0001), an acceleration of treatment initiation by nearly 2 hours. These findings demonstrated that prehospital delivery of experimental neuroprotective therapy was feasible and achieved accelerated treatment start. Though additional logistical effort was required, it was clearly justified by the much greater volumes of salvageable brain tissue accessed.

On the basis of these findings, we proposed, and the NIH was kind enough to fund, a pivotal prehospital study: the FAST-MAG Phase 3 trial. The Phase 3 trial has two objectives: to demonstrate that paramedic initiation of the neuroprotective agent magnesium sulfate in the field is an efficacious and safe treatment for acute stroke and to show that field enrollment and treatment of acute stroke patients is a practical and feasible strategy for Phase 3 stroke trials, permitting enrollment of greater numbers of patients in hyperacute time windows.

FAST-MAG Phase 3 is a placebo-controlled, double-blind, randomized trial. Patients are enrolled in the field within 2 hours of last known well time. The magnesium sulfate dose being tested, a 4-g load in the field over 15 minutes followed by a 16-g maintenance infusion in hospital over 24 hours, is in the low-to-middle range of that typically used in preeclampsia/eclampsia. FAST-MAG Phase 3 enrolled its first patient in January 2005. As of the time of this lecture in February 2012, we have enrolled 1470 (83%) of the planned 1700 patients, and expect to complete accrual by the end of 2012.

Like all Phase 3 acute stroke trials, FAST-MAG is Big Science but with a regional twist. Similar to many trials performed in the prehospital system, FAST-MAG Phase 3 is a multicenter but single-region study, employing the EMS of Los Angeles and Orange Counties, including all receiving stroke center hospitals to which they transport patients. Fully 353 rescue ambulances are carrying study drug and screening all transports to 59 receiving hospitals for study-eligible patients. Our terrific core of 15 fulltime FAST-MAG nurses has trained 3300 paramedics in study procedures. Over 570 emergency physicians and over 160 neurologists, neurosurgeons, and hospitalists at receiving hospitals are serving as study investigators.

Although study outcomes remain under blind, the FAST-MAG investigators are able to share baseline data...
characterizing the study subjects enrolled to date, which provide an important first glimpse at what patients in a prehospital focal stroke trial look like (Table 1). The average age and sex ratio are typical for acute stroke. The qualifying event is acute cerebral ischemia in over 70% of the patients and acute intracranial hemorrhage in nearly one fourth. The rate of stroke mimics is reassuringly low at 4%, below the 5% allowed for in our sample size calculations.

Most important are the study treatment start times to date in the baseline FAST-MAG Phase 3 trial. The median time interval from last well known well to start of study drug is 46 minutes. More than 7 of every 10 patients in the trial are being treated within the first 60 minutes after last known well time—the golden hour. It is striking to compare this enrollment in the earliest time period with that achieved in the hospital-based neuroprotective trials in the early 2000s. Although they enrolled over 5300 patients, these trials enrolled only 10 patients within 60 minutes of the last known well time.5 So far in FAST-MAG, we have enrolled over 1070 patients in the first 60 minutes, a 100-fold increase in treatment in the golden hour.

Accordingly, FAST-MAG is well along the way to accomplishing several innovations in acute stroke trial research. FAST-MAG will be the first acute stroke trial in which neuroprotective agents are delivered before recanalization therapies, testing the long cherished, but never before tested, vision of using neuroprotectives to “freeze” the penumbra in time to treat the preponderance of patients in the first, golden, hour after onset. Whether FAST-MAG succeeds in showing specific benefit of magnesium sulfate or in only demonstrating the feasibility of prehospital therapy delivery, the ability to treat patients swiftly, as swiftly as the biology of brain ischemia demands, is now in our grasp.

### Table 1. Characteristics of First 1470 FAST-MAG Phase 3 Trial Patients

<table>
<thead>
<tr>
<th>Demographics and stroke severity</th>
<th>69 (39–95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics and stroke severity</td>
<td>69 (39–95)</td>
</tr>
<tr>
<td>Age, mean (range)</td>
<td>69 (39–95)</td>
</tr>
<tr>
<td>Female</td>
<td>42%</td>
</tr>
<tr>
<td>Median field LAMS score</td>
<td>4</td>
</tr>
<tr>
<td>Median arrival NIHSS</td>
<td>9</td>
</tr>
<tr>
<td>Stroke type</td>
<td></td>
</tr>
<tr>
<td>Cerebral ischemia</td>
<td>72%</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>24%</td>
</tr>
<tr>
<td>Other (stroke mimics)</td>
<td>4%</td>
</tr>
<tr>
<td>Enrollment mechanisms</td>
<td></td>
</tr>
<tr>
<td>Explicit self-consent</td>
<td>59%</td>
</tr>
<tr>
<td>Explicit proxy consent</td>
<td>39%</td>
</tr>
<tr>
<td>Exception from explicit consent</td>
<td>2%</td>
</tr>
<tr>
<td>Key treatment intervals</td>
<td></td>
</tr>
<tr>
<td>Median interval last known well to study drug (m)</td>
<td>46</td>
</tr>
<tr>
<td>Mean interval paramedics on scene to study drug (m)</td>
<td>25</td>
</tr>
<tr>
<td>Mean interval paramedics on scene to ED (m)</td>
<td>35</td>
</tr>
<tr>
<td>Study drug started in golden hour (15–60 min after LKW)</td>
<td>73%</td>
</tr>
<tr>
<td>Study drug started 61–120 min after LKW</td>
<td>24%</td>
</tr>
</tbody>
</table>

ED indicates emergency department; LAMS, Los Angeles Motor Scale; LKW, last known well time; and NIHSS, National Institutes of Health Stroke Scale.

onset, in which thrombolytics are effective. Most importantly, FAST-MAG will be the first acute stroke trial of any therapy type to treat the preponderance of patients in the first, golden, hour after onset. Whether FAST-MAG succeeds in showing specific benefit of magnesium sulfate or in only demonstrating the feasibility of prehospital therapy delivery, the ability to treat patients swiftly, as swiftly as the biology of brain ischemia demands, is now in our grasp.

### Treatment Sure: Highly Effective Endovascular Recanalization

Although neuroprotection is intrinsically a temporizing therapy, enabling brain cells to tolerate an ischemic episode longer, reperfusion is intrinsically a definitive therapy, finally resolving the ischemic episode. In ischemic stroke, neuroprotection can be treatment swift, but only recanalization can be treatment sure. Accordingly, it is heartening that a substantial advance in brain reperfusion therapy is occurring at the same time as progress in prehospital neuroprotection. In 2012, we stand poised on the threshold of a new era of acute cerebral reperfusion therapy—the era of highly effective cerebral recanalization.

A variety of treatment strategies burgeoned in the first period of clinical practice of cerebral recanalization, from 1995 to 2010, including IV fibrinolysis within 3 and then 4.5 hours of onset, intra-arterial fibrinolysis up to 6 hours of onset, mechanical thrombectomy up to 8 hours after onset, and acute angioplasty and stenting. Investigators learned that the best approach to endovascular treatment depends on the nature of the target occlusion. When the patient has in situ intracranial atherosclerosis with a small degree of supervening thrombosis (the same lesion cardiologists typically treat in acute myocardial infarction), the best approach is angioplasty with or without stenting, cracking the hard plaque open. However, when the patient has an embolus, a thrombus that has landed in a relatively normal recipient vessel after forming in a cardiac, transcardiac, or arterial donor site, then thrombus retrieval devices and thrombus aspiration devices are the best approach. Sometimes the obstructing thrombi are quite small. Because the main stem of the middle cerebral artery is only 3 mm in diameter, a small embolic clot can obstruct the middle cerebral artery and cause a devastating hemispherical syndrome. But other times, the target occlusions are huge clot snakes, 15 cm or more, running the entire length of the cervical and intracranial internal carotid artery and the proximal middle and anterior cerebral arteries. A purely chemical strategy, using IV or intra-arterial fibrinolysis, is highly unlikely to digest such a huge clot burden in a useful time frame. Mechanical thrombectomy devices are much better at debulking large proximal thrombi than are lytic drugs.

However, despite these advances in pathophysiological understanding, the little-appreciated, but well-documented, fact is that our first-generation recanalization treatments are actually not very good at reopening occluded cerebral arteries.27 IV TPA achieves partial recanalization in only 40% of cases and complete recanalization in only 5% of cases.28 With IV TPA, we are delivering a therapy that fails to open the target artery more often than it succeeds. Endovascular
recanalization therapies perform somewhat better, but still substantially below optimal performance criteria. In registration trials, intra-arterial fibrinolysis, coil retriever therapy, and aspiration device therapy each achieved partial recanalization in more than six tenths of patients but complete recanalization in less than one quarter of treated cases.\textsuperscript{20-23} It is instructive, and chastening, to compare progress made by stroke physicians in achieving reperfusion in acute brain ischemia with that of cardiologists in achieving reperfusion in acute myocardial ischemia over the past 30 years. Cardiologists rapidly evolved from IV fibrinolysis to endovascular angioplasty and stenting and now completely recanalize 80% to 95% of their patients. In contrast, stroke physicians have until recently remained mired in the 20% to 25% complete recanalization rate range.

But, this year, our capabilities are changing dramatically, with the arrival in clinical practice of a new class of mechanical thrombectomy devices—the stent retrievers. When these retractable stents are deployed into target thrombi, they push the clot against the vessel wall, immediately restoring blood flow. Their crossing struts then sink in to engage the clot at multiple points of contact, enabling them to pull the clot out of the artery with substantially greater efficiency than first-generation thrombectomy devices. Examples of stent retrievers approved in some parts of the world are the Solitaire Flow Restoration device (Covidien), the Trevo device (Stryker), the Revive device (Johnson and Johnson), and the ReStore device (Reverse Medical). In open clinical series, the stent retrievers have performed far more effectively at achieving recanalization than prior cerebral thrombectomy approaches.\textsuperscript{23-28} For example, across the first 8 reported series enrolling 196 patients, the Solitaire device achieved partial recanalization in 93% patients and complete recanalization in 66% patients. For the first time, stroke physicians in the cerebral circulation are approaching the same acute recanalization range that cardiologists achieve in the coronary circulation (Figure 3).

The first two randomized clinical trials comparing stent retrievers with the Food and Drug Administration’s regulatory standard first-generation device, the Merci coil retriever, have been reported and confirm a major advance in care. Both studies showed such major treatment arm differences in favor of the stent retrievers that early stopping rules were triggered. In the Solitaire With the Intention for Thrombectomy (SWIFT) trial, core laboratory-adjudicated recanalization rates were substantially higher with Solitaire than with Merci (thrombolysis in myocardial infarction successful recanalization partial or better, 69% versus 30%, \(P=0.0001\)).\textsuperscript{35} In the Thrombectomy Revascularization of Large Vessel Occlusions in Acute Ischemic Stroke (TREVO2) trial, the Trevo device similarly outperformed the Merci device (thrombolysis in cerebral infarction, TICI, partial or better, 86% versus 60%, \(P=0.00001\)).\textsuperscript{28} Clinical outcome differences paralleled the recanalization rate differences. In SWIFT, good neurological outcome was more frequent at 3 months with Solitaire than with Merci (58% versus 33%, \(P=0.017\)) and mortality was reduced (17% versus 38%, \(P=0.02\)). In TREVO2, functional independence at 3 months was better with Trevo than with Merci (40% versus 22%, \(P=0.013\)), although mortality was nominally increased (34% versus 24%, \(P=0.18\)).

As a result of these trials, the Food and Drug Administration cleared the Solitaire and Trevo devices for marketing in the United States in 2012. With the release of stent retrievers in the United States as well as Europe, stroke physicians, for the first time in history of cerebrovascular therapeutics, now have a recanalization therapy that will completely recanalize target arteries in more than half of the cases and partially in more than 80%. We can for the first time pursue recanalization therapy confident that we will succeed at least in opening the occluded vessel, the great preponderance of time. At the most basic level of therapeutic success, restoring vessel patency, treatment sure is now a reality.

Reopening occluded arteries is a necessary, but not sufficient, condition for achieving good clinical outcomes with recanalization therapy. If the entire tissue at risk has already progressed to irreversible infarction, reperfusion will be futile, and may even cause harm by increasing the risk of hemorrhagic transformation. Accordingly, another aspect of treatment sure is reliably identifying patients who still harbor substantial penumbral tissue and have already evolved only a modest core, and so will definitely benefit if reperfusion is achieved. Although within the first 2 hours of onset, virtually every large artery occlusion patient still has a favorable penumbral pattern, between 3 and 14 hours, an increasing proportion of patients have completed their infarct and will no longer benefit from intervention. Over the past decade, several investigative groups around the world have been steadily refining our ability to use multimodel magnetic resonance imaging or computed tomography imaging to identify later-presenting patients with salvageable tissue and select them for recanalization therapy. Multicenter clinical trials testing and refining imaging selection have included the Diffusion and Perfusion
Imaging Evaluation for Understanding Stroke Evaluation (DEFUSE), Echoplanar Imaging Thrombolytic Evaluation (EPITHET), and Desmoteplase in Acute Ischemic Stroke/Dose Escalation of Desmoteplase in Acute Ischemic Stroke (DIAS/DEDAS) trials of IV fibrinolysis and the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) trial of endovascular mechanical thrombectomy.27–40

The NIH MR RESCUE, led by my colleagues Chelsea Kidwell and Reza Jahan, is prospectively validating MR imaging selection criteria developed in an open series at University of California, Los Angeles (UCLA) and computed tomography imaging selection criteria developed in a multicenter open series at Virginia and Pittsburgh. In the open series, multimodal baseline imaging was performed in consecutive patients who subsequently underwent endovascular reperfusion therapy.41

To identify the pretreatment imaging parameters that predicted tissue salvage with reperfusion or tissue infarction despite reperfusion, we performed voxel-by-voxel fate mapping of evolution of tissue state among the subgroup of patients in whom recanalization was achieved. Multivariate analysis identified the combination of imaging parameters that best distinguished infarct core from ischemic penumbra. Then, to identify the patients likely to benefit from therapy, we investigated the core and penumbra volume thresholds that predicted which patients would and would not achieve functional independence if reperfusion was achieved. We next developed an automatic processing program, Rescue On Site, that analyzes baseline imaging and classifies all tissue voxels with reduced blood flow as infarct core, threatened penumbra, or benign oligemia and assigns patients to favorable or unfavorable penumbral pattern categories. In MR RESCUE, patients ineligible for or having failed IV TPA undergo automated penumbral imaging at baseline. Then, stratified by their penumbral pattern, they are randomized to endovascular therapy or medical care alone.

MR RESCUE will not only be the first trial of imaging selection for neurothrombectomy; it will also be the first randomized trial of any sort to compare endovascular mechanical thrombectomy with supportive medical care in IV TPA ineligible patients or IV TPA failures. Accordingly, it will contribute to another aspect of treatment sure—placing our treatments on the firm foundation of unequivocal clinical trial evidence. Neurothrombectomy devices were first cleared for use in the United States and abroad along a device pathway, not as treatments proven to make patients better. Only randomized trials against standard, noninterventional medical care can demonstrate the clinical efficacy of neurothrombectomy interventions. The recent disappointing results of the NIH IMS 3 trial have demonstrated that first-generation endovascular recanalization treatments, when compared with IV TPA alone soon after TPA treatment start, were not as clinically efficacious as widely believed. An alternative way forward is to perform a randomized trial in a different population than enrolled in IMS 3, one containing patients certain to have target occlusions, to not be eligible or responsive to TPA, and to have penumbral tissue that can be salvaged. The MR RESCUE trial is such a study, and we are happy to report that in April 2012, MR RESCUE performed the exit clinical visit for its 120th and final patient. In a few short months, data and imaging analysis will be complete, the blind will be broken, and we will have data from the first-ever randomized trial of neurothrombectomy versus supportive care in acute ischemic strokes with persisting vascular occlusions to guide our clinical decision making.

Another important dimension of treatment sure is assuring that all patients have access to effective acute stroke care. As we stand poised on the brink of a new era of highly effective endovascular cerebral recanalization, we need to redesign our regional systems of acute stroke care to ensure that we can deliver acute neurothrombectomy therapies to all the patients who may benefit from them. Over the past decade, we have made tremendous progress in building out an essentially one-tier regional system that ensures transport of acute stroke patients by the prehospital EMS to Primary Stroke Centers (PSCs) where IV TPA can be delivered rapidly and reliably.42 As of 2012, there are now over 1000 certified PSCs in the United States. From 2000 to 2011, more and more US states and counties passed legislation or regulations directing ambulances to route patients directly to certified PSCs. As a result, by the start of 2012, 20 states and several additional counties were routing patients directly to the stroke centers. Because these include most of the high population states, 54% of Americans now live in a jurisdiction that, when they call 911, they will be brought directly to a certified stroke center.

It is now time to begin building out a second level of care in our regional acute stroke systems: a Comprehensive Stroke Center (CSC) tier that preferentially routes appropriate patients to hospitals capable of delivering the new highly effective endovascular recanalization devices. The best arrangements of CSC hubs and PSC and acute stroke ready hospital spokes will vary in different geographic regions, depending on population density, topographical transportation barriers, and facility capabilities. Sometimes, it will make sense for EMS to route directly from the field to CSC patients likely harboring large artery occlusions and in the field to stabilize threatened brain early, followed by IV TPA. Other times, the best approach will be a streamlined process of interfacility transfer to CSCs from first sites of care at PSCs or acute stroke ready hospitals. The effort to develop a national network of CSCs is well under way, with national recommendations for CSCs issued by the Brain Attack Coalition,43,44 performance measures for CSCs endorsed by the American Heart Association/American Stroke Association (AHA/ASA),45 and a certification process for CSCs launched by the Joint Commission. Over the course of 2012–2014, in the United States and abroad, a system of CSCs will be implemented on the ground, enabling us to treat vastly more patients than at present with the new, powerful, and highly effective neurothrombectomy recanalization devices.

Version 1.0 of acute ischemic stroke care in the recanalization era was focused around delivery of a therapy of intermediate effectiveness (IV TPA) in an intermediate time frame. Version 2.0 will retain IV TPA as an element but with crucial expansions of neuroprotective therapy before and highly effective mechanical thrombectomy afterward (Table 2). Patients will receive neuroprotective agents in the field to salvage and stabilize the brain early followed by IV TPA on hospital (or mobile hospital) arrival. TPA failure patients will be treated with highly effective recanalization devices so that all patients
will have open arteries when they are admitted to systematic care in a Stroke Unit. As a result, ideally all of our patients will have excellent outcomes.

When I first became a stroke translational investigator, 20 years ago, seamlessly combined neuroprotective and reperfusion therapy for acute ischemic stroke was a hazy communal dream among stroke physicians. Journeying along the path to its realization with my collaborators, the field in general, and our patients, has been an exciting and rewarding privilege. I firmly believe that we now, at long last, stand poised on the threshold of the time when this vision becomes an everyday clinical reality, and all acute ischemic stroke patients will benefit from treatment swift and treatment sure.

Sources of Funding
Portions of the work described in this lecture have been supported by the National Institutes of Health and the American Heart Association.

Disclosures
The University of California, Regents receive funding for Dr Saver's services as a scientific consultant regarding trial design and conduct to Coviden, CoAxia, BrainsGate, Genervon, and Telerics. Dr Saver is an investigator in the NIH FAST-MAG, MR RESCUE, CLEAR-ER, and IMS 3 multicenter clinical trials for which the UC Regents receive payments on the basis of clinical trial performance; has served as an unpaid site investigator in multicenter trials run by Lundbeck and Covidien for which the UC Regents receive payments on the basis of clinical trial performance; has served as a scientific consultant regarding trial design and conduct to Covidien and is an employee of the University of California.


Key Words: ischemic stroke • neuroprotection • recanalization • reperfusion • thrombectomy
The 2012 Feinberg Lecture: Treatment Swift and Treatment Sure
Jeffrey L. Saver

Stroke. 2013;44:270-277; originally published online December 13, 2012;
doi: 10.1161/STROKEAHA.112.671354
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/44/1/270

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/