Fifty Years of Acute Ischemic Stroke Treatment: A Personal History

James C. Grotta

Stroke Research and Mobile Stroke Unit, Memorial Hermann Hospital-Texas Medical Center, Houston, TX, USA

Keywords

Stroke · History · Cerebral blood flow · Neuroprotection · Thrombolysis · Mobile stroke unit

Abstract

Background: It has been 50 years since the first explorations of the physiology of cerebral ischemia by measuring cerebral blood flow (CBF), and 25 years since the approval of tissue plasminogen activator for treating acute ischemic stroke. My personal career began and matured during those eras. Here, I provide my perspective on the evolution of acute stroke research and treatment from 1971 to the present, with some in-depth discussion of the National Institutes of Neurologic Disease and Stroke (NINDS) tissue-type plasminogen activator (tPA) stroke trial and development of mobile stroke units. **Summary:** Studies of CBF and metabolism in acute stroke patients revealed graded tissue injury that was dependent on the duration of ischemia. Subsequent animal research unraveled the biochemical cascade of events occurring at the cellular level after cerebral ischemia. After a decade of failed translation, the development of a relatively safe thrombolytic allowed us to achieve reperfusion and apply the lessons from earlier research to achieve positive clinical results. The successful conduct of the NINDS tPA stroke study coupled with positive outcomes from companion tPA

studies around the world created the specialty of vascular neurology. This was followed by an avalanche of research in imaging, a focus on enhancing reperfusion through thrombectomy, and improving delivery of faster treatment culminating in mobile stroke units. **Key Messages:** The last half century has seen the birth and evolution of successful acute stroke treatment. More research is needed in developing new drugs and catheters to build on the advances we have already made with reperfusion and also in evolving our systems of care to get more patients treated more quickly in the prehospital setting. The history of stroke treatment over the last 50 years exemplifies that medical “science” is an evolving discipline worth an entire career’s dedication. What was impossible 50 years ago is today’s standard of care, what we claim as dogma today will be laughed at a decade from now, and what appears currently impossible will be tomorrow’s realities.

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Introduction

“Until today, stroke was an untreatable disease” [1]. Those were my words to the press on December 14, 1995, when the National Institutes of Neurologic Disease and Stroke tissue-type plasminogen activator (NINDS tPA)

study results were published. Most young vascular neurologists think that acute stroke treatment began that day and are familiar with the great strides since which have been successful in 2 general spheres: (1) improving implementation by tailoring and enhancing health-care services and public education and (2) enhancing reperfusion by technological advances in imaging and endovascular therapy. But before the older generation disappears and the details and chronology forgotten, for the record let's summarize how we got to that date in 1995, and what were the immediate and subsequent consequences. Perhaps there are lessons to be learned and people who should be recognized with the caveat that this reflection is colored heavily by my own personal perspective and professional journey, and by no means is meant to minimize the contribution of many giants in the field or the importance of numerous seminal papers that are not mentioned.

Ancient History of Stroke

Before effective treatment could even be considered, the pathophysiology needed to be understood. It may be hard to believe, but medical students in the 1960s were not instructed in stroke etiology because it was not until the clinicopathological correlations of Fisher and Adams [2] building on earlier pathological observations [3] that identified atherosclerosis and associated atherothrombosis and atheroembolism, as well as small vessel lipohyalinosis as the cause of most strokes. Older notions of vasospasm and hemodynamic causes were recognized as much less common. This led to the adoption of anticoagulation with heparin in the hopes of arresting the formation of these clots [4]. In the absence of other therapeutic options, and also in the absence of a tradition of randomized trials, heparin treatment was adhered to conceptually and vigorously. In fact, anticoagulation was not tested in a large properly powered randomized acute stroke trial until heparin was shown to be ineffective in the International Stroke Trial [5] and heparinoid in the TOAST trial [6]. It was only after those studies were published in 1997–98 that anticoagulation was finally put to rest as a routine acute stroke treatment.

Most of the advances in stroke care in the 1970s and 80s were not in acute stroke treatment but rather in prevention, and while not the focus of this review, a few landmarks should be mentioned because these were the first prospective multicenter randomized trials that became the model for all future clinical research in stroke. These

include the first trials demonstrating successful prevention of strokes by aspirin, and subsequent studies of dipyridamole, ticlopidine, and later clopidogrel [7–12], and of carotid endarterectomy [13–15]. The important partnership with vascular surgery deserves recognition for the successful completion of those studies. Starting in the 1970s, data emanating from the visionary Framingham Study [16] led to the recognition of cardioembolism from atrial fibrillation as an important cause of stroke, and subsequent very successful randomized trials of secondary prevention with anticoagulation [17, 18]. These successes established the tradition of randomized trials, the discipline of clinical trial design, and the engagement of the NINDS.

The idea that ischemic stroke could actually be treated and reversed was a dream that had no scientific basis until we learned how to measure cerebral blood flow (CBF) and metabolism. In 1965, Ingvar and Lassen [19] adopted the Kety and Schmidt [20] method, developed back in 1945, to first measure regional CBF in man. Many studies of CBF and later metabolism in stroke patients were then carried out in the 1970s [21–25], first using Xenon-133, and then Oxygen-15, Nitrogen-13, and 18-Fluorodeoxyglucose positron emission tomography. Investigators showed regional reductions in CBF distal to occluded arteries, loss of autoregulation, and recognized that CBF was reduced in a graded fashion, and that various CBF thresholds existed from core to what is now recognized as penumbra [26]. Increased oxygen extraction was documented in these penumbral regions, suggesting that viable tissue (and function) might be salvaged if CBF could be restored [25]. That was my introduction to the field as a fellow in Cerebral Blood Flow and Metabolism at Massachusetts General Hospital under the late Bob Ackerman, and why my perspective on the history of acute stroke treatment begins about 50 years ago (Fig. 1). At around the same time, a study in awake primates with transient middle cerebral artery (MCA) occlusion demonstrated that CBF reduction to 10–20 cm³/100 gm/min as seen in “penumbral” regions could be withstood for up to 2–3 h before infarction occurred, and that no matter how profound the reduction in CBF, little infarction occurred if the occlusion was released within the first hour [27]. This seminal study was followed by many other animal model studies demonstrating the time dependence of reperfusion. Many criticisms have been aimed at animal stroke models and their failure to translate to clinical results, but with reperfusion, as we will see, the animal models closely predicted what we have observed in our clinical trials.

Fig. 1. a Patient breathing positron-emitting oxygen-15 (O-15) on the Massachusetts General Hospital Positron Emission Tomography (PET) scanner in 1978. **b** PET scan using O-15 of a patient with left carotid occlusion. Left column showing relative reduced uptake of O-15 labelled water indicating reduced CBF in the left hemisphere compared to the right. Middle column showing comparable utilization of inhaled O-15 labelled oxygen indicating equal rate of oxygen utilization in both hemispheres. Right column showing calculated increased rate of oxygen extraction from the blood in the left hemisphere compared to the right. Taken together,

these findings suggest left brain ischemia (low CBF and increased oxygen extraction) but not infarction (preserved oxygen utilization). **c** Depiction of the relationship of cerebral MR as measured by 18-fluorodeoxyglucose (x axis) and CBF as measured by Nitrogen-13 (y axis) in acute stroke using PET [24]. Measurements below or to the left of the zero lines represent decreased CBF or MR, respectively, and increased CBF or MR if above the zero lines. Of interest is the recognition of preserved MR and low CBF (mismatch) in very early stroke. CBF, cerebral blood flow; MR, metabolic rate; PET, positron emission tomography.

The “Middle Ages” of Stroke Treatment

Various efforts were made to raise CBF in controlled laboratory circumstances including raising CO_2 by breathing carbogen gas, vasodilators such as nitroglycerine, and pressors. CO_2 and vasodilators were not widely tested since the vasculature was already maximally vasodilated in ischemic regions. On the other hand, when MAP was raised acutely, we saw striking increases in CBF in ischemic regions that had lost their autoregulatory capacity. Pressors were never thoroughly tested in randomized trials, though a small clinical series [28] suggested their benefit in selected cases, and of course, they are still used in the critical care environment in certain circumstances of hemodynamic crisis.

The first acute stroke treatment to be widely tested in prospective multicenter clinical trials was hemodilution

(HD). HD was an attempt to improve CBF based on an understanding of blood viscosity and the notion that diluting the blood and lowering viscosity would improve its rheology [29]. Also, it was postulated that hypervolemia might also raise CBF by improving cardiac output since Swan-Ganz studies of stroke patients arriving in the ED demonstrated volume depletion [30].

Clinical trials were carried out in the United States and in Europe of HD accomplished by phlebotomy and fluid replacement either by crystalloids (isovolemic) or volume expanders such as dextran or hetastarch (hypervolemic) [31–33]. These studies all failed, probably because the intervention was too late, had offsetting negative systemic hemodynamic effects, and most importantly did not remove the underlying cause of the problem – the offending obstruction. But the studies had a more impor-

tant enduring benefit; they established the tradition, practice, and leadership of clinical trials for acute stroke. At the recent retirement of his associate Werner Hacke, Helmut Zeumer, who was the first to carry out intra-arterial treatment of a basilar occlusion [34], pointed out that the HD studies seeded the acute stroke treatment clinical trial infrastructure and vetted many of the clinical trial investigators who went on to lead the thrombolysis trials in their more mature years.

In parallel with studies of CBF and metabolism, other investigators turned to animal models to better understand the pathophysiology of ischemic stroke at the molecular level. Rodent models of global and then focal ischemia were established and perfected in several labs [35–42]. Initially, these models were developed mainly for nonclinical scientific reasons and succeeded in revealing the “ischemic cascade” of pivotal events triggered by an interruption of CBF, starting with perturbed calcium homeostasis, excitotoxicity, free radical generation, altered cell signaling in the neurovascular unit, and a host of other downstream events. This discovery, and the subsequent observations that infarct volume and motor deficits in rats could be reduced by blocking some of these steps pharmacologically, led to dreams of an effective stroke treatment that might be translated to virtually any stroke patient, and perhaps even be effective for acute brain injury resulting from trauma or hemorrhage.

Throughout the 1980s and early 90s, acute stroke therapy and professional meetings were all about curing strokes in rats, which proved remarkably easy to do by cleverly identifying or creating pharmaceuticals that could target and ameliorate steps along the “ischemic cascade.” We were unravelling ischemic neurotoxicity, and it seemed certain that we would be able to translate this molecular knowledge to clinical efficacy. An optimistic review article on acute stroke therapy appeared in the *New England Journal of Medicine (NEJM)* [43]. Enthusiastically, and in retrospect naively, many investigators and virtually every pharmaceutical company went about the business of conducting large clinical trials attempting to translate laboratory to bedside success. Millions of NIH and pharmaceutical dollars, and years of work in the lab and at the bedside unfortunately did not result in an effective “neuroprotective” drug. These studies have been reviewed elsewhere [44] and their reasons for failure debated, but one thing is certain – they cemented the tradition of clinical research in stroke, created the training environment for the first stroke clinical research coordinators, and brought in financial support for stroke programs

throughout the world. They have also established the search for an effective acute stroke therapy as the number one priority of the stroke community.

A few points should be emphasized that were learned in the process of searching for effective neuroprotection. First that these were complex drugs targeting a vulnerable and unstable organ system; drugs targeting biochemical events at the neuronal level were bound to have behavioral side effects most notably the glutamate antagonists [45, 46], and others targeting the vasculature such as calcium antagonists had hypotensive effects [47, 48]. Second, these studies were hard to carry out, requiring dedicated clinical research staff including research coordinators. Recruitment of patients was difficult and almost always lagged behind projections. Results often differed across the Atlantic or Pacific [49–51]. Potentially effective drugs that did not have pharmaceutical company support were abandoned [52]. The STAIR meetings were established to bring rigor and standardization to both preclinical and clinical aspects, and perceived shortcomings of earlier studies were addressed [53]. This included bringing treatment into the prehospital arena in the FastMag study [54], and “dirty” approaches targeting multiple pathways such as hypothermia [55]. Although even these efforts have failed, neuroprotection is still a concept that is being explored particularly with earlier treatment and directly linked to reperfusion. Furthermore, the search for neuroprotection succeeded in fostering a more sophisticated understanding of clinical trial design, interactions with the FDA and CMS, as well as the aforementioned clinical trial infrastructure within the stroke community. In a sense, acute stroke clinical trial research was “born” with HD, “grew up” with neuroprotection, and “got married” to thrombolysis.

The Stroke “Renaissance”: Thrombolysis and the NINDS tPA Stroke Study

“What do you think of tPA?” was a question asked of me by John Marler in 1988. My response – “what is tPA?” I was trained in a fellowship in CBF and metabolism, was PI of one the early HD trials, and ran a laboratory studying transient MCA occlusion and reperfusion, but therapeutically was focused on neuroprotection. So, I was unaware of the work of Desire Collen who discovered tPA [56], Diane Pennica at Genentech who cloned the drug in the early 1980s, only dimly aware of its use in myocardial infarction, and oblivious that lytics had been tried to open occluded carotid and basilar arteries [34, 57, 58]. While I

was studying neuroprotection, I did not fully appreciate the significance of the seminal early animal studies with lytics by Zivin et al. [38] and Del Zoppo et al. [59]. I highly recommend the entertaining book by the late Justin Zivin on the early development of tPA [60]. Fortunately, others were more perceptive. Mike Walker and John Marler, the stroke director and associate director respectively at NINDS, were convinced to fund Brott et al. [61, 62] to treat patients in the pilot trials of IV tPA. In the meantime, Furlan partnered with Higashida and Wechsler to start an intra-arterial trial with pro-Urokinase [63], Mori et al. [64] conducted a small randomized trial of a lower dose of tPA in Japan, and Hacke, Kaste, Fieschi, and their European colleagues began *European Cooperative Acute Stroke Study* (ECASS), a study of a higher dose of tPA with a 6-h time window [65]. It should be noted that all of these studies eventually turned out to be positive if not at first, then in their second iteration, but as a participant in the NINDS trial, I can elaborate on that historic study [66].

I will go into some detail about a few of the novel “nuts and bolts” of the NINDS tPA study execution [67] that I believe were critical to the trial’s success in achieving efficient start-up, speedy treatment, enthusiastic engagement of the investigators, and completion of enrollment on schedule. The NINDS tPA studies were partly “investigator initiated” but a “top down” approach emanating from NINDS was pivotal to its organization and start-up, and its eventual success. The study germinated from the NINDS “Master Agreements” that NINDS leadership created in the mid-1980s. They requested that centers who wanted to do stroke clinical trials form agreements with NINDS outlining their qualifications. Sometime during the pilot tPA studies, around 1988, NINDS sent around a Request For Protocols to do a clinical trial of thrombolytics. The request didn’t specify tPA and did not even ask for a protocol – it said that the protocol would be developed by NINDS and the investigators chosen to carry out the project, and that the response should emphasize the center’s ability to access and treat acute stroke patients quickly. That was when I approached Paul Pepe, the Houston Fire Department Emergency Medical Services (EMS) medical director, to help. His office provided us with the statistics on which hospitals in the city were receiving the most acute stroke patients, and agreed to arrange notification of our stroke team when a stroke patient was en route by EMS to the ED of any of them. A critical component of the success of the trial, and our being awarded one of the contracts to carry out what became part 1 of the NINDS tPA stroke

study, was effective collaboration with EMS, and agreement of most of the competing hospitals in the city to cooperate.

At the first investigators’ meeting, the site PIs sat around the table and hashed out the protocol. We excluded Genentech from involvement in the study design or management, other than supplying the drug. The site PIs divided up the difficult parts of the protocol design. My job was to come up with recommendations about reocclusion and what to do about concomitant antithrombotic drugs. I reviewed whatever literature existed about clot propagation or reocclusion in stroke (essentially no reliable data), and in acute MI, and concluded that since there had been no effective ways to achieve recanalization in the brain, we did not know if reocclusion after recanalization would be a problem. We decided to err on the side of safety and not allow anticoagulants or antiplatelets for 24 h post-tPA in order to minimize any risk of bleeding, but also to build in a clinical observation sub-study to look for deterioration after improvement as a marker for recanalization followed by reocclusion [68]. I also wanted to build CBF measurements before and after tPA into the protocol using SPECT to document reperfusion. This was “allowed” but there was little enthusiasm and we were the only center that documented reperfusion following intravenous tPA in acute stroke patients [69]. Barbara Tilley PhD, the Principle Investigator of the Data Core, did an outstanding job orchestrating the study. When she came to Houston and asked us to flowchart in detail each and every step patients went through in each of our 8 participating hospital emergency departments, labs, and CT areas, both Patti Bratina RN our lead coordinator and I thought it was “overkill.” But the technique worked in identifying sources of delay and it’s something I remind the fellows to do before they start any project, including when we started the mobile stroke unit (MSU) project that has loads of similarities. Linda Greenberg RN, a seasoned ED nurse, became our “patient recruitment coordinator.” This was a unique job description for a clinical trial, with the main charge to figure out ways to assure fast and frequent patient enrollment. She recognized the possibility to use the EMS telemetry center to notify us when an HFD ambulance was en route to one of our hospitals with a stroke patient. That was the beginning of the practice of advanced notification to hospital EDs of stroke patients, which even now saves so much time once the patient arrives. During the trial, we would make trips to the EMS telemetry center every few weeks to take them donuts and remind them to call us and carried out in-services to the paramedics between shifts at 6:00 a.m. every few

months to remind them to call telemetry whenever they picked up a stroke patient. On tPA “runs,” Linda helped us negotiate the EDs reminding us that we were visitors in their territory, and also helped gain the trust of the paramedics most of whom she knew from her job as an ED nurse.

At our site, each stroke team member carried a pager that was alerted by EMS telemetry whenever EMS was en route with a probable acute stroke patient to one of the 8 participating EDs. Tom DeGraba arrived as a stroke fellow in 1989, only a few months after we started the NINDS tPA study and I also received help from subsequent fellows (Sandy Hanson, Cindy Sills, Mark Fisher, and Lewis Morgenstern). We (me or one of the fellows) and a nurse were on call 24/7 from 1989 to 1995 and slept with the beeper by our beds. We did not yet have cell phones – throughout the trial we had to carry around quarters and use pay phones if we were not at home or in our office. When we got a page, we would call the ED doc and the CT tech to alert them, and head right to the ED. We instituted the pager code “86” based on our youthful jobs as waiters and waitresses to call off the alert if we learned the patient did not meet inclusion criteria. I cannot remember our site’s exact enrollment rate but think it was about 2 per week. We did not keep a log of alerts, but my recollection is that our alert-to-treatment ratio was about 5:1, for example, ~2 alerts/day. Because we were only alerted after the paramedics had decided to transport the patient as a stroke, the alert-to-treatment ratio was lower (but also later) than the 10:1 ratio on the MSU where we are alerted based on the initial 911 call. As the trial proceeded, we got better at determining the time of onset using “anchors” to help the family recall associated events such as what program was on the TV. The concept of using the time “last known well” to conservatively estimate an uncertain stroke onset time evolved during the trial. Once we arrived at the ED, we would do everything ourselves to determine eligibility and get treatment started as quickly as possible. This included pushing the patient to the CT scanner (in those days not in the ED; usually on another floor or even a different building), hand-carrying the blood to the lab and waiting for the results, and mixing and administering the study drug. We hardly ever had a patient refuse consent but it did happen. Although we excluded patients with obvious and extensive hypodensity on CT, we did not screen for subtle signs of early ischemia or strictly observe the “1/3 MCA rule” [70] until after ECASS was published in the last year of our study [65]. We were strict about inclusion and exclusion criteria and obtaining a platelet count and Prothrombin Time (this

was before INR became commonly used), and excluding patients with recent surgery and bleeding, etc. Because the risk of bleeding in stroke mimics was unknown, we were careful only to include patients we were pretty sure were not mimics. The median NIHSS score was around 14 – there were few mimics included. The one area where our site pushed the envelope a bit was BP treatment. Because of our experience with Nicardipine in the lab and clinically [48], we were an early proponent of its use to smoothly control BP by continuous IV infusion. The protocol precluded “aggressive” treatment of BP prior to enrollment but did allow labetalol and drugs that could be easily titrated. The intent was to avoid precipitous drops in BP as often occurred with sublingual Nifedipine that was in common use at the time in emergency departments. The investigators finally agreed to allow Nicardipine but the other centers did not use it as much. We stored the study drug and placebo in identical boxes in a locked fishing tackle box in each ED with a sealed envelope containing the number of the next box of drug to use. Each site had its own randomization sequence. Study enrollment did not occur until the bolus was actually given. The placebo looked exactly like the real drug – there was no way to tell. It was a constant effort to get patients treated within 90 min, since we could not enroll more than 2 additional patients in the 91- to 180-min time window than we had in 0–90 min. We often had to let a 91–180 pt go until we had an additional 0–90 pt. We would all look at our watch when we treated and if it was close to 90 min, we went with the watch that read the earliest. Almost all our “<90” min patients were treated at 80–90 min.

It was only after we gave the drug if the patients had gum bleeding or rarely angioedema (which we did not know about before the study) that we had a hint they must have received tPA. It was clear that some patients were dramatically improving and of course a few bled. But these observations were so much earlier after the stroke ictus than had ever before been clearly chronicled that we really could not be at all sure if what we were seeing was spontaneous or due to the tPA. We were also scrupulous that the 90-day outcome be carried out by an investigator not involved in the patient’s care. So I do not believe investigator bias influenced study results. It was stressful, but it was a “rush” and fun to treat patients. We always hung around for a few hours to see if the patient got better or bled. Sometimes I am surprised at how blasé some of our trainees are after giving tPA. With regard to minor strokes, we included only a few with mild deficits, including a man with just severe hand weakness, but not those with just sensory symptoms or a minimal dysarthria. I

remember not enrolling a few I thought were too mild, and the next day seeing them with deficits that I wished I had treated. I also remember our first hemorrhage – a young man with a big MCA stroke that dramatically improved posttreatment. It was a weekend morning enrollment, and several hours later the fellow (Tom DeGraba) called me while I was biking to tell me the patient bled and died. I still think of that case since understanding why he bled would be the key to limiting complications. Why had he gotten all better only then to bleed? Was the vascular endothelium even more vulnerable than the neurons? It was tough being blinded but we all sensed we were onto something big – it felt like we were the “Mercury astronauts” of stroke. I fondly remember the personalities of my coinvestigator colleagues and the esprit de corps we developed throughout the study. There was a friendly competition among all of us to enroll the most patients. The investigator calls that occurred every 2 weeks were something I never wanted to miss.

When Part 1 ended, we were not told the results. We knew it was a Phase 2b study with safety and 24-h NIHSS as the primary outcome, but designed to be followed by a confirmatory phase 3 study (Part 2) with long-term outcome since we knew we would need 2 trials for FDA approval. We were encouraged by our anecdotal experience of seeing some patients dramatically improve, and by the fact that since Part 1 was not stopped, it must be safe. The investigators were asked if we wanted to look at the results. We said not to unblind us if the DSMB thought we should go on to do the Phase 3 efficacy study. We wanted a minimum of interruption to avoid dismantling the patient recruitment apparatus that we had each developed at our respective centers. However, there was some disagreement on this point, and, in retrospect, perhaps the 2 studies would have been seen more as 2 independent studies if reported separately. We were told by the DSMB simply to “redo” part 1 but using a 3-month outcome looking for a “consistent and persuasive” difference between the groups. Hence, Barbara Tilley came up with the “Global Statistic” combining the modified Rankin Scale, Barthel Index, NIHSS, and Glasgow Outcome Scale into one metric [71]. Part 2 was completed in 2 years.

All the investigators and coordinators were invited to attend the data presentation meeting at Airlie, a rural retreat in Virginia. When Dr. Tilley put up the neutral results of the prespecified outcome for Part 1 (difference in proportion of patients achieving a 4-point improvement in NIHSS by 24 h), we felt deflated. But then she showed that the 4-point threshold was too easy a target and that using an improvement by any cutpoint above 4 points

was positive for tPA [72]. And then, like an orchestra conductor building her coda to a climactic ending, she put up a transparency with 4 aces. We were confused until she replaced the aces with the positive data for each component of the Global Statistic for both Part 2 and Part 1 (Fig. 2). There was a collective gasp, and then cheering and euphoria as she showed slide after slide of the outcomes in Part 2 and Part 1, all showing consistent positive results without high rates of bleeding. I walked outside at the break into a clear Fall afternoon, looked up and saw an ultralight flying overhead. I knew the stroke world had changed forever. Many times during the trial and after, even when I would have to get up in the middle of the night or leave dinner or a ballgame to treat a patient, I knew I was doing what I was meant to do with my career. This vascular neurologist is at his best when giving tPA. We decided to write up the paper then and there and divided up the tasks. At first, we could not figure out the best way to show the mRS results, and I came up with the idea of a bar with segments for each unit on the scale sized proportionately to the percent of patients. I think I had seen it used before, but I was immediately credited by the group as creating the “Grotta bars” – an appellation that sticks to this day. We wrote the paper in 1 day and left the meeting with a rough draft.

The Airlie meeting was in the early fall, and we were sworn to secrecy. The paper came out on December 5, 1995. A press conference was organized. I was asked to make the initial statement to the press and was coached the night before to come up with something catchy. I came up with “Until today stroke was an untreatable disease,” and it was picked up as the quote of the day in the New York times. My 5 s of fame!! I came back to Houston, and there was an impromptu faculty meeting that gave me a standing ovation – that remains in my memory as one of the most gratifying moments of my career!! At the International Stroke Conference that year in San Antonio, after presentation of the main results, I gave a short perspective talk showing the relative risks and benefits compared to other treatments. Later that year, the FDA reviewed the data; Harold Adams, who had been PI of the heparinoid trial [6] chaired the committee that made the recommendation to the FDA to approve the drug.

The NINDS tPA results were, sadly and frustratingly, not universally accepted as the investigators had expected and hoped. While there were early supporters among the stroke leadership [73, 74], other leaders of the stroke community, rather than embracing the treatment, complained that we had done a clinical trial of reperfusion without delineation of the underlying vascular pathology

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Table 4. Outcomes at Three Months According to the Time to Treatment after the Onset of Stroke.

ASSESSMENT INSTRUMENT	PERCENTAGE WITH FAVORABLE OUTCOME*		ODDS RATIO (95% CI)†	RELATIVE RISK (95% CI)‡	P VALUE
	t-PA	PLACEBO			
Part 2, 0-180 min§					
No. of patients	168	165			
Global test	—	—	1.7 (1.2-2.6)	—	0.008
Barthel index	50	38	1.6 (1.1-2.5)	1.3 (1.0-1.7)	0.026
Modified Rankin scale	39	26	1.7 (1.1-2.6)	1.5 (1.1-2.0)	0.019
Glasgow outcome scale	44	32	1.6 (1.1-2.5)	1.4 (1.0-1.8)	0.025
NIHSS	31	20	1.7 (1.0-2.8)	1.5 (1.0-2.2)	0.033
Part 1, 0-180 min§§					
No. of patients	144	147			
Global test	—	—	2.1 (1.3-3.2)	—	0.001
Barthel index	54	39	1.8 (1.1-2.8)	1.4 (1.1-1.8)	0.012
Modified Rankin scale	47	27	2.3 (1.4-3.6)	1.7 (1.3-2.3)	<0.001
Glasgow outcome scale	47	31	2.0 (1.2-3.1)	1.5 (1.1-2.0)	0.005
NIHSS	38	21	2.2 (1.3-3.7)	1.8 (1.2-2.6)	0.002
Combined results§					
0-90 min§					
No. of patients	157	145			
Global test	—	—	1.9 (1.2-2.9)	—	0.005
Barthel index	53	38	1.8 (1.2-2.9)	1.4 (1.1-1.8)	0.010
Modified Rankin scale	40	28	1.7 (1.0-2.6)	1.4 (1.0-1.9)	0.035
Glasgow outcome scale	43	32	1.6 (1.0-2.5)	1.3 (1.0-1.8)	0.057
NIHSS	34	20	2.0 (1.2-3.4)	1.7 (1.1-2.5)	0.008
91-180 min§					
No. of patients	155	167			
Global test	—	—	1.9 (1.3-2.9)	—	0.002
Barthel index	51	38	1.6 (1.1-2.5)	1.3 (1.0-1.7)	0.026
Modified Rankin scale	45	25	2.4 (1.5-3.7)	1.8 (1.3-2.4)	<0.001
Glasgow outcome scale	47	30	2.0 (1.3-3.2)	1.6 (1.2-2.1)	0.002
NIHSS	34	21	2.0 (1.2-3.2)	1.6 (1.1-2.3)	0.008

* Scores of 95 or 100 on the Barthel index, <1 on the NIHSS and modified Rankin scale, and 1 on the Glasgow outcome scale were considered to indicate a favorable outcome in this intention-to-treat analysis.

†The Mantel-Haenszel test was used for univariate analyses with groups stratified according to clinical center and, for analyses of the 0-to-180-minute groups, the time to treatment after the onset of stroke (0 to 90 minutes or 91 to 180 minutes). For the global test (which used log-linear functions), the same stratifying variables were included as covariates. CI denotes confidence interval.

‡Time to treatment after the onset of stroke.

§The results for part 1 were considered hypothesis-generating. The definition of favorable outcome was derived from part 1 data and required testing in part 2.

b

Fig. 2. a NINDS stroke study investigators at Airlie Virginia, 1994. **b** Table from the original publication [66] showing consistent positive results in parts 1 and 2 of the NINDS stroke study on all outcome measures in patients treated within 90 min and 91-180 min

of onset. **c** Graphic representation of the proportional distribution of modified Rankin scale scores in the tPA and placebo groups on all 4 outcome measures [66]. NINDS, National Institutes of Neurologic Disease and Stroke.

[75]. I had written a 10-year update of current stroke treatment, but the *NEJM* editors preferred a debate. I objected since we had completed a prospective randomized trial showing tPA was beneficial and safe if given quickly without extensive preliminary imaging, and I thought that those who advocated a different approach needed to prove it in a clinical trial before their argument received equal credibility to the NINDS results [76]. As it turns out, the approach used in the NINDS trial for selecting patients for tPA has endured, though my colleagues' approach to first document arterial occlusion turned out to be correct for endovascular therapy. The European stroke community was also initially reticent to embrace the NINDS study results since their study (ECASS [65]) had been neutral (though positive if they confined their observation to the 0–3 h patients), and also because of the concomitant negative Streptokinase trials [77–80] which in addition to the longer time window used a more dangerous drug, a larger dose, and coupled it with heparin. At the biannual International Symposium on Thrombolytic Therapy in Acute Ischemic Stroke held in Copenhagen in 1996, most of the European attendees did not think tPA should be considered standard of care within 3 h of symptom onset until Marku Kaste stood up and asked – “if you had a stroke within 3 h, raise your hand if you would want to get tPA” and everyone raised their hands. The European Medicines Agency conditionally approved tPA in 2002 based on the 0–3-h results in ECASS II [81], but it was not until the Safe Implementation of Thrombolysis in Stroke-Monitoring Study registry results [82], and ECASS III showing benefit out to 4.5 h [83] that tPA became widely embraced in Europe. There was also resistance among the general Neurology community. I got many calls and messages from neurologists saying I had “ruined their lives” now that they had to get up in the middle of the night and treat stroke patients. They had a point – most neurologists didn't go into neurology to do emergency care in the middle of the night, and furthermore there was no professional reimbursement for the added effort. Fortunately, the stroke center movement and development of stroke teams helped abate that resistance. In my opinion, the AAN could have fought harder and earlier for appropriate reimbursement to professionals who had to do the work of evaluating and treating stroke patients 24/7. Finally, although each of the NINDS study sites included Emergency Medicine leadership (many of whom subsequently led the first study to test combined IV and IA tPA [84]), there was vitriolic resistance by many in the Emergency Medicine community who levelled untrue attacks that the study and investiga-

tors were influenced by Genentech, and that the results were not accurately presented [85–87], fueled by taking pieces of the data and reanalyzing them to make their points. They even hired an investigative reporter to write up an attack on the study and its investigators, which unbelievably got published in the *BMJ* [88]. We were particularly irked by the conflict of interest issue. Genentech did provide honoraria to the investigators after the drug was FDA approved to give educational lectures to neurologists and Emergency Medicine physicians about the results. The company also had to reanalyze the data (and came up with the same results) for their presentation to the FDA for drug approval. However, of all the studies I have carried out, the NINDS tPA stroke trials had less industry involvement than any. As far as the data issue was concerned, among the skeptics' unfounded attacks, they did uncover one important fact, that there was an imbalance between the tPA and placebo groups in stroke severity. This imbalance, and that more severe strokes arrived in the ED earlier, initially prevented us from seeing the relationship of time from stroke onset to treatment and response to tPA. When we adjusted for these imbalances, the inverse relationship of treatment benefit to time elapsed became more evident [89]. Nevertheless, despite additional trial data and pooled analyses of 6,756 patients from all randomized trials [90, 91], and an independent reanalysis of the NINDS study data [92], all supporting the use of tPA, there remains resistance among some ED physicians. Furthermore, despite best intentions and 2 decades of effort, it has been impossible to recreate the rapid treatment in the ED that we achieved in the NINDS trial, with the minority of patients treated within 90 min of onset, extremely few within the first hour [93], and many qualified patients not treated at all. Hence, the rationale for MSUs.

The Post-tPA Years

The importance of the success of tPA treatment for the development of the field of Vascular Neurology and stroke care in general cannot be over-emphasized. First, the adoption of tPA into mainstream stroke therapy caused a resurgence of interest in the field of stroke and the need for subspecialty training and certification, resulting in a proliferation of stroke fellows, fellowship programs, and Vascular Neurology certification. Second, it created a need for more and better acute stroke services in the prehospital, ED, and in-patient realms. Separate stroke services and stroke units became common. It also

Fig. 3. TCD signals from the MCA in a patient with acute ischemic stroke treated with tPA [99]. (Middle) Artist drawing of clot fragmentation, dissolution, and reformation correlating with TCD signals. (Bottom) Corresponding NIHSS and Time. MCA, middle cerebral artery; TCD, transcranial doppler.

resulted in greater involvement of neurologists in the field of neurocritical care since tPA-treated patients often were initially admitted to the ICU and neurologists assumed more “ownership” of the patients they had treated. This helped stimulate neurocritical care subspecialty fellowship programs among Neurology trainees. Third, since tPA treatment required patients to seek care urgently, and for first responders to recognize stroke, community and paramedic education projects on stroke recognition and response were instituted with modest success [94, 95]. At the same time, important disparities in stroke care were recognized, and now that we had effective therapy, efforts were born to try to overcome them [96–98].

A fourth huge effect of tPA was the recognition that reperfusion was the key to better stroke outcomes, thus stimulating efforts to build on tPA success with more effective reperfusion methods. In Houston, Alexandrov began routine continuous transcranial doppler monitoring of tPA-treated patients and was able to detect the dynamic nature of M1 clot dissolution, distal embolization, and sometimes reocclusion [99] (Fig. 3), helping us understand the frequent failure of tPA alone to recanalize these large clots, and the need for more aggressive measures. This led to efforts to augment clot lysis using continuously applied ultrasound [100], and more recently, once clinicians became more comfortable with the safety of tPA, efforts to add antithrombotic therapy [101]. And, of course, of even greater importance and future success, the prematurely abandoned efforts to approach these large clots by endovascular means and administration of intra-arterial lytics [63] were replaced by attempts to mechanically disrupt them. The subsequent evolution from mechanical clot disruption to the MERCI catheter and eventually to present-day aspiration devices and stent retrievers, and the clinical trials which at first were frus-

tratingly neutral but then overwhelmingly positive, requires a separate manuscript. We will not discuss endovascular therapy further here aside from saying that the most important 2 factors resulting in eventual positive results were when the technology of stent retrievers caught up to the clinical need for speedy atraumatic clot extraction, and when clinical trial selection criteria, enabled by the widespread availability of CT angiography, became focused on the LVO patients most likely to benefit.

Along this line, a fifth impact of tPA was fostering the development of brain imaging paradigms to select patients for treatment. Because of the need to exclude hemorrhage before tPA treatment, CT became the “EKG of stroke,” and CT scanners proliferated to most EDs. The Calgary group developed the ASPECTS score [102]. In parallel, the Stanford group showed that magnetic resonance diffusion imaging could identify early infarction [103], and perfusion techniques could identify ischemic and oligemic regions [104]. Now that we could open up arteries with tPA and catheters, investigators began the long hard work of sequential studies in such patients to identify what variables and parameters predicted response to therapy. This led to the rediscovery that such penumbral tissue can be present many hours after stroke onset [25, 105] leading to a dual approach to stroke treatment that still exists; the “time is brain” concept based on the finding from each and every trial of thrombolysis that clinical outcomes are better with earlier treatment [89, 91, 93], and the “every brain is different” concept that variability in clot size, location, and collateral flow determines how the slope of time versus response can vary from individual to individual [106–108].

Mobile Stroke and the “Golden Hour” as Target

The MSU, an ambulance equipped with a CT scanner, personnel, and drugs to treat a patient with tPA on scene, was introduced by Fassbender et al. [109] (Fig. 4). Conceptually, a MSU is an ED on wheels that allows us to recreate in patients what we learned from animal models that reperfusion in the first “golden” hour has the potential to reduce stroke volume and subsequent disability to a minimum. My own involvement with MSUs was, as with tPA, somewhat serendipitous. In 2012, one of our European visiting stroke fellows drew my attention to Fassbender’s work, and the next year Heinrich Audebert reported faster treatment with his Berlin MSU at the International Stroke Conference [110]. Recognizing that we

Fig. 4. Outside (a) and inside (b) including the ceretom CT scanner (c) of the first mobile stroke unit in Homberg Germany [109].

could recreate the template we used in the NINDS study by having the MSU stroke team, in collaboration with EMS, control the selection and treatment of patients, and yet do it even faster in the prehospital setting rather than in the ED, it seemed to be a natural fit for us to try in Houston. It also coincided with a natural transition in my own career. I had accomplished most of my goals on the faculty at UT medical school where I had created and run the stroke service since 1979 and had just completed 8 years as departmental chair, and I wanted a new challenge. At the age of 69, I realized that I should focus on things I already knew how to do well and what I enjoyed the most. That was doing clinical research and treating acute stroke patients with tPA. When I floated the idea of putting a MSU in operation and doing a clinical trial to test its benefits before a few potential donors, one was willing to provide the money, and another the ambulance, to get us started! Within 9 months, with the assistance of Stephanie Parker RN as Program Director, in May 2014 we launched the Houston MSU, the first in the United States [111]. After a brief run-in phase, in collaboration with Jose-Miguel Yamal, PhD and Suja Rajan, PhD at the UT School of Public Health, we designed and commenced the Benefits of Stroke Treatment with a Mobile Stroke Unit Compared to Standard Management by Emergency Medical Services (BEST-MSU, NCT 02190500), a prospective comparative effectiveness study of MSU versus standard management by alternating weeks when the MSU was in service versus EMS management without the MSU. We followed all patients for a full year measuring clinical outcomes and health-care utilization. We obtained funding from the American Heart As-

sociation and showed that having the physician oversee patient selection and treatment by telemedicine was as accurate and fast as doing it on-board [112, 113]. Eventually, we were successful in obtaining funding from the Patient Centered Outcomes Institute to enlarge the study to 7 centers with sufficient statistical power to detect a clinically important effect.

In the meantime, the Berlin group was completing their own series of MSU studies [114]. Their final results were published in early 2021 [115] showing faster and more frequent treatment and better clinical outcome with MSU. Our study completed enrollment in August 2020 and the results published in September 2021 [116]. We were able to treat 33% of tPA-eligible patients within the first “golden hour” compared to only 3% with standard EMS/ED management, and average time to tPA bolus was 36 min faster with the MSU. EMS/ED treatment was not only slower, but also many eligible patients did not ever get treated in the ED. Of patients who were independently adjudicated as meeting all criteria for tPA treatment, 97% received tPA in the MSU group compared to only 80% with EMS/ED management. This faster and more frequent MSU treatment translated to better clinical outcomes with the main impact in patients returning completely back to their baseline state; an absolute increase of 11% achieving a 90-day modified Rankin Scale of 0 or 1. Furthermore, speedier and more frequent MSU treatment was not due to less accuracy in diagnosis; only 9% of treated patients in each group were finally diagnosed as stroke mimics, none of whom had any bleeding as a result of their treatment. These positive results were driven by the patients treated in the first hour. As seen in

Fig. 5. Time from last known normal to tPA bolus versus percentage of patients with 90-day mRS 0–1 (MSU + Standard Management patients combined) in the BEST-MSU study [116]. Correlation between time and 90-day ordinal mRS (Spearman correlation coefficient 0.15, $p < 0.001$). Correlation between 1-h treatment and 90-day mRS 0–1 (Fisher’s exact test $p = 0.007$). tPA, tissue-type plasminogen activator; MSU, mobile stroke unit; BEST-MSU; Benefits of Stroke Treatment with a Mobile Stroke Unit Compared to Standard Management by Emergency Medical Services.

Figure 5, and also demonstrated in data from the Get With the Guidelines registry [93], the slope of the inverse relationship between the frequency of such excellent outcomes and amount of time elapsed from stroke onset (e.g., the duration of the occlusion) becomes more steep in that first hour. This exactly reflects the original primate studies of MCA occlusion [27]. Since we included in our study over 20% of patients who had a baseline mRS of >1 and could not reach a final value of 0.1, probably 70% of patients treated within the first hour after symptom onset will return to their baseline state. The results suggest that acute ischemic stroke in the first hour after occlusion is a different pathophysiology from strokes seen later in their course; not only has the brain suffered less permanent damage, but clots are fresher and easier to lyse [117].

Conclusion and Questions for the Next 50 Years

The last half century has seen the birth and evolution of successful acute stroke treatment. The 3 broad pillars that have enabled this progress are an understanding that infarction can be prevented by timely reperfusion, the ability to quickly image the brain and vasculature, and the development of drugs and catheters to get the artery open, all supported by carefully designed translational clinical research. Where do we go from here? More research is

certainly needed in developing new drugs and catheters to build on the success we have already obtained. However, the MSU data show that getting more patients treated within the first “golden hour” would have even greater impact. This argues for innovative research and alteration of our systems of care to get more patients treated in the prehospital setting.

How do we accomplish this? First, more patients and caregivers need to call for, and receive, help right away. Why don’t patients or caregivers call 911 immediately? Education is not enough. We need to remove the financial and practical disincentives of calling for help, create stroke “hot-lines” which can utilize home-based telecommunications to immediately triage concerning symptoms, and reorganize our response systems to be more user-friendly and nimble at distinguishing between true emergencies such as acute stroke, and less urgent matters. Second, we need to explore the concept of early warning devices to avoid relying on brain injured patients to initiate the call for help. Finally, we need to include prehospital stroke treatment in our stroke systems of care just as we have done with emergency department management. Prehospital stroke treatment is now evidence based, and should be appropriately reimbursed, included in our stroke guidelines, and required of every comprehensive stroke center as part of their certification.

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Conflict of Interest Statement

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References

- Grotta JC. The New York Times. 1995 May 12.
- Fisher CM, Adams RD. Cerebrovascular diseases. Neuropathological progress. *Listing Res Cardiovasc Field*. 1964;10:425–6.
- Huthinson EC, Acheson E. *Stroke*. WB Saunders; 1975.
- Millikan CH, Siekert RG, Whisnant JP. Anticoagulant therapy in cerebrovascular disease: current status. *JAMA*. 1958;166:587–91.
- The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. *Lancet*. 1997;349:1569–81.
- Low molecular weight heparinoid, ORG 10172 (danaparoid), and outcome after acute ischemic stroke. A randomized, controlled trial. The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. *JAMA*. 1998;279:1265–72.
- Fields WS, Lemak NA, Frankowski RF, Hardy RJ. Controlled trial of aspirin in cerebral ischemia. *Stroke*. 1977;8:301–14.
- The Canadian Cooperative Study Group. A randomized trial of aspirin and sulfinpyrazone in threatened stroke. *N Engl J Med*. 1978;299:53–9.
- Boussier MG, Eschwege E, Haguenu M, Lefaucconier JM, Thibault N, Touboul D, et al. “AICLA” controlled trial of aspirin and dipyridamole in the secondary prevention of athero-thrombotic cerebral ischemia. *Stroke*. 1983;14:5–14.
- Gent M, Blakely JA, Easton JD, Ellis DJ, Hachinski VC, Harbison JW, et al. The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. *Lancet*. 1989;1:1215–20.
- Hass WK, Easton JD, Adams HP Jr, Pryse-Phillips W, Molony BA, Anderson S, et al. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. Ticlopidine Aspirin Stroke Study Group. *N Engl J Med*. 1989;321:501–7.
- CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348:1329–39.
- Eastcott HH, Pickering GW, Rob CG. Reconstruction of internal carotid artery in a patient with intermittent attacks of hemiplegia. *Lancet*. 1954;267:994–6.
- Fields WS, North RR, Hass WK, Galbraith JG, Wylie, Ratnov G, et al. Joint study of extracranial arterial occlusion as a cause of stroke. I. Organization of study and survey of patient population. *JAMA*. 1968;203(11):955–60.
- Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med*. 1998;339:1415–25.
- Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22:983–8.
- The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med*. 1990;323:1505–11.
- The Stroke Prevention in Atrial Fibrillation Study Group Investigators. Stroke prevention in atrial fibrillation study: final results. *Circulation*. 1991;84:527–39.
- Ingvar DH, Lassen NA. Methods for cerebral blood flow measurements in man. *Br J Anaesth*. 1965;37:216–24.
- Kety SS, Schmidt CF. The determination of cerebral blood flow in man by the use of nitrous oxide in low concentrations. *Am J Physiol*. 1945;143:53–66.
- Høedt-Rasmussen K, Skinhoj E, Paulson O, Ewald J, Bjerrum JK, Fahrenkrug A, et al. Regional cerebral blood flow in acute apoplexy. The “luxury perfusion syndrome” of brain tissue. *Arch Neurol*. 1967;17:271–81.
- Meyer JS, Kanda T, Fukuuchi Y, Shimazu K, Dennis EW, Ericsson AD. Clinical prognosis correlated with hemispheric blood flow in cerebral infarction. *Stroke*. 1971;2:383–94.
- Reivich M, Kuhl D, Wolf A, Greenberg A, Phelps M, Ido T, et al. The (18F) fluorodeoxyglucose method for the measurement of local cerebral glucose utilization in man. *Circ Res*. 1979;44:127–37.
- Kuhl DE, Phelps ME, Kowell AP, Metter EJ, Selin C, Winter J. Effects of stroke on local cerebral metabolism and perfusion: mapping by emission computed tomography of 18FDG and 13NH3. *Ann Neurol*. 1980;8:47–60.
- Ackerman RH, Correia JA, Alpert NM, Baron JC, Gouliamos A, Grotta JC, et al. Positron imaging in ischemic stroke disease using compounds labeled with oxygen 15. Initial results of clinicophysiological correlations. *Arch Neurol*. 1981;38:537–43.
- Astrup J, Siesjö BK, Symon L. Thresholds in cerebral ischemia – the ischemic penumbra. *Stroke*. 1981;12:723–5.
- Jones TH, Morawetz RB, Crowell RM, Marcoux FW, FitzGibbon SJ, DeGirolami U, et al. Thresholds of focal cerebral ischemia in awake monkeys. *J Neurosurg*. 1981;54:773–82.
- Rordorf G, Koroshetz WJ, Ezzeddine MA, Segal AZ, Buonanno FS. A pilot study of drug induced hypertension for treatment of acute stroke. *Neurol*. 2001;56:1210–3.
- Grotta J, Ackerman R, Correia J, Fallick G, Chang J. Whole blood viscosity parameters and cerebral blood flow. *Stroke*. 1982;13:296–301.
- Grotta JC, Pettigrew LC, Allen S, Tonnesen A, Yatsu FM, Gray J, et al. Baseline hemodynamic state and response to hemodilution in patients with acute cerebral ischemia. *Stroke*. 1985;16:790–5.
- Multicenter trial of hemodilution in acute ischemic stroke: results of subgroup analyses. Scandinavian Stroke Study Group. *Stroke*. 1988;19:464–71.
- Haemodilution in acute stroke: results of the Italian haemodilution trial. Italian Acute Stroke Study Group. *Lancet*. 1988;1:318–21.
- Hypervolemic hemodilution treatment of acute stroke: results of a randomized multicenter trial using pentastarch. The Hemodilution in Stroke Study Group. *Stroke*. 1989;20:317–23.
- Zeumer H, Hacke W, Kolmann HL, Poock K. Local fibrinolysis in basilar artery thrombosis. *Dtsch Med Wochenschr*. 1982;107:728–31.
- Pulsinelli WA, Brierley JB. A new model of bilateral hemispheric ischemia in the unanesthetized rat. *Stroke*. 1979;10:267–72.
- Ginsberg MD, Lockwood AH, Busto R, Finn RD, Butler CM, Cendan IE, et al. A simplified in vivo autoradiographic strategy for the determination of regional cerebral blood flow by positron emission tomography: theoretical considerations and validation studies in the rat. *J Cereb Blood Flow Metab*. 1982;2:89–98.
- Simon RP, Swan JH, Griffiths T, Meldrum BS. Blockade of N-methyl-D-aspartate receptors may protect against ischemic damage in the brain. *Science*. 1984;226:850–2.
- Zivin JA, Fisher M, DeGirolami U, Hemenway CC, Stashak JA. Tissue plasminogen activator reduces neurological damage after cerebral embolism. *Science*. 1985;230:1289–92.
- Choi DW, Maulucci-Gedde MA, Kriegstein AR. Glutamate neurotoxicity in cortical cell culture. *J Neurosci*. 1987;7:357–68.
- Brint S, Jacewicz M, Kiessling M, Tanabe J, Pulsinelli W. Focal brain ischemia in the rat: method for reproducible neocortical infarction using tandem occlusion of the distal middle cerebral and ipsilateral common carotid arteries. *J Cereb Blood Flow Metab*. 1988;8:474–85.
- Chopp M, Chen H, Vande Linde AM, Brown E, Welch KM. Time course of postischemic intracellular alkalosis reflects the duration of ischemia. *J Cereb Blood Flow Metab*. 1990;10:860–5.
- DeGraba TJ, Ostrow PT, Grotta JC. Threshold of calcium disturbances after focal cerebral ischemia in rats. Implications of the window of therapeutic opportunity. *Stroke*. 1993;24:1212–6.
- Grotta JC. Current medical and surgical therapies for cerebrovascular disease. *New Eng J Med*. 1987;317:1505–16.
- Gonzales NR, Grotta JC. Pharmacologic modification of acute cerebral ischemia. In: Grotta JC, Albers GW, Broderick JP, Day AL, Kasner SE, Lo EH, et al., editors. *Stroke pathophysiology, diagnosis, and management*. 7th ed. New York: Elsevier; 2021.

- 45 Grotta J, Clark W, Coull B, Pettigrew LC, Mackay B, Goldstein LB, et al. Safety and tolerability of the glutamate antagonist CGS 19755 (Selfotel) in patients with acute ischemic stroke. Results of a phase IIa randomized trial. *Stroke*. 1995;26:602–5.
- 46 Albers GW, Atkinson RP, Kelley RE, Rosenbaum DM. Safety, tolerability, and pharmacokinetics of the N-methyl-D-aspartate antagonist dextrorphan in patients with acute stroke. Dextrorphan Study Group. *Stroke*. 1995;26:254–8.
- 47 Randomised, double-blind, placebo-controlled trial of nimodipine in acute stroke. Trust Study Group. *Lancet*. 1990;336:1205–9.
- 48 Rosenbaum D, Grotta J, Yatsu F, Picone C, Pettigrew LC, Bratina P, et al. Pilot study of nicardipine for acute ischemic stroke. *Angiology*. 1990;41:1017–22.
- 49 Grotta J. Lubeluzole treatment of acute ischemic stroke. The US and Canadian Lubeluzole Ischemic Stroke Study Group. *Stroke*. 1997;28:2338–46.
- 50 Feuerstein GZ, Zaleska MM, Krams M, Wang X, Day M, Rutkowski JL, et al. Missing steps in the STAIR case: a translational medicine perspective on the development of NXY-059 for treatment of acute ischemic stroke. *J Cereb Blood Flow Metab*. 2008;28:217–9.
- 51 Kern R, Nagayama M, Toyoda K, Steiner T, Hennerici MG, Shinohara Y. Comparison of the European and Japanese guidelines for the management of ischemic stroke. *Cerebrovasc Dis*. 2013;35:402–18.
- 52 Piriyaawat P, Labiche LA, Burgin WS, Aronowski JA, Grotta JC. Pilot dose-escalation study of caffeine plus ethanol (Caffeinol) in acute ischemic stroke. *Stroke*. 2003;34:1242–5.
- 53 Stroke Therapy Academic Industry Roundtable II (STAIR-II). Recommendations for clinical trial evaluation of acute stroke therapies. *Stroke*. 2001;32:1598–606.
- 54 Saver JL, Starkman S, Eckstein M, Stratton SJ, Pratt FD, Hamilton S, et al. Prehospital use of magnesium sulfate as neuroprotection in acute stroke. *N Engl J Med*. 2015;372:528–36.
- 55 Lyden P, Hemmen T, Grotta J, Rapp K, Ernstrom K, Rzesiewicz, et al.; Collaborators. Results of the ICTuS 2 trial (intravascular cooling in the treatment of stroke 2). *Stroke*. 2016;47:2888–95.
- 56 Collen D. On the regulation and control of fibrinolysis. *Thromb Haemost*. 1980;43:77–89.
- 57 Sussman BJ, Fitch TS. Thrombolysis with fibrinolysin in cerebral arterial occlusion. *JAMA*. 1958;167:1705–9.
- 58 Herndon RM, Meyer JS, Johnson JF, Landers J. Treatment of cerebrovascular thrombosis with fibrinolysin. Preliminary report. *Am J Cardiol*. 1960;6:540–5.
- 59 Del Zoppo GJ, Copeland BR, Waltz TA, Zy-roff J, Plow EF, Harker LA. The beneficial effect of intracarotid urokinase on acute stroke in a baboon model. *Stroke*. 1986;17:638–43.
- 60 Zivin JA. *tPA for stroke*. New York: Oxford University Press; 2011.
- 61 Brott TG, Haley EC Jr, Levy DE, Barsan W, Broderick J, Sheppard GL, et al. Urgent therapy for stroke. Part I. Pilot study of tissue plasminogen activator administered within 90 minutes. *Stroke*. 1992;23:632–40.
- 62 Haley EC Jr, Levy DE, Brott TG, Sheppard GL, Wong MC, Kongable GL, et al. Urgent therapy for stroke. Part II. Pilot study of tissue plasminogen activator administered 91–180 minutes from onset. *Stroke*. 1992;23:641–5.
- 63 Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, et al. Intra-arterial prourokinase for acute ischemic stroke. The PRO-ACT II study: a randomized controlled trial. Prolyse in acute cerebral thromboembolism. *JAMA*. 1999;282:2003–11.
- 64 Mori E, Yoneda Y, Tabuchi M, Yoshida T, Ohkawa S, Ohsumi Y, et al. Intravenous recombinant tissue plasminogen activator in acute carotid artery territory stroke. *Neurology*. 1992;42:976–82.
- 65 Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). *JAMA*. 1995;274:1017–25.
- 66 National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *New England J Med*. 1995;333:1581–7.
- 67 A systems approach to immediate evaluation and management of hyperacute stroke. Experience at eight centers and implications for community practice and patient care. The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group. *Stroke*. 1997;28:1530–40.
- 68 Grotta JC, Welch KMA, Fagan SC, Lu M, Frankel MR, Brott T, et al. Clinical deterioration following improvement in the NINDS rt-PA stroke trial. *Stroke*. 2001;32:661–8.
- 69 Grotta J, Alexandrov A. tPA-associated reperfusion after acute stroke demonstrated by SPECT. *Stroke*. 1998;29:429–32.
- 70 von Kummer R, Meyding-Lamadé U, Forsting M, Rosin L, Rieke K, Hacke W, et al. Sensitivity and prognostic value of early CT in occlusion of the middle cerebral artery trunk. *Am J Neuroradiol*. 1994;15:9–15.
- 71 Tilley B, Marler J, Geller N, Lu M, Legler J, Brott T, et al. Use of a global test for multiple outcomes in stroke trials with application to the National Institute of Neurological Disorders and Stroke t-PA Stroke Trial. *Stroke*. 1996;27:2136–42.
- 72 Haley EC, Lewandowski C, Tilley BC. Myths regarding the NINDS rt-PA stroke trial: setting the record straight. *Ann Emerg Med*. 1997;30:676–82.
- 73 Saver JL, Starkman S. State of the art medical management of acute ischemic stroke. *J Stroke Cerebrovasc Dis*. 1997;6:189–94.
- 74 Davis SM, Donnan GA. Thrombolysis for acute stroke. *J Clin Neurosci*. 1997;4:1–2.
- 75 Caplan LR, Mohr JP, Kistler JP, Koroshetz W. Should thrombolytic therapy be the first-line treatment for acute ischemic stroke? Thrombolysis – not a panacea for ischemic stroke. *N Engl J Med*. 1997;337:1309–10.
- 76 Grotta J. t-PA – the best current option for most patients. *NEJM*. 1997;337:1310–2.
- 77 Hommel M, Boissel J-P, Cornu C, Boutitie F, Lees KR, Besson G, et al. Termination of trial of streptokinase in severe acute ischaemic stroke. *Lancet*. 1995;345:57.
- 78 Donnan GA, Davis SM, Chambers BR, Gates PC, Hankey GJ, McNeil JJ, et al. Trials of streptokinase in severe acute ischaemic stroke. *Lancet*. 1995;345:578–9.
- 79 Randomised controlled trial of streptokinase, aspirin, and combination of both in treatment of acute ischaemic stroke. Multicentre Acute Stroke Trial – Italy (MAST-I) Group. *Lancet*. 1995;346:1509–14.
- 80 The Multicenter Acute Stroke Trial – Europe Study Group; Hommel M, Cornu C, Boutitie F, Boissel JP. Thrombolytic therapy with streptokinase in acute ischemic stroke. *N Engl J Med*. 1996;335:145–50.
- 81 Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. *Lancet*. 1998;352:1245–51.
- 82 Wahlgren N, Ahmed N, Davalos A, Grond M, Hacke W, Hennerici MG, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet*. 2007;369:275–82.
- 83 Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359:1317–29.
- 84 Lewandowski C, Frankel M, Tomsick T, Broderick J, Frey J, Clark W, et al. Combined intravenous and intra-arterial r-TPA versus intra-arterial therapy of acute ischemic stroke: emergency management of stroke (EMS) bridging trial. *Stroke*. 1999;30:2598–605.
- 85 Hoffman JR. Should physicians give tPA to patients with acute ischemic stroke? Against: and just what is the emperor of stroke wearing? *West J Med*. 2000;173:149–50.
- 86 Mann J. An open letter to the stroke interventionalist community and truths about the NINDS study: setting the record straight. *West J Med*. 2002;176:192–4.
- 87 Trotter G. Why were the benefits of TPA exaggerated? *West J Med*. 2002;176:194–7.
- 88 Lenzer J. Alteplase for stroke: money and optimistic claims buttress the “brain attack” campaign. *BMJ*. 2002;324:723–9.

- 89 Marler JR, Tilley BC, Lu M, Brott TG, Lyden PC, Grotta JC, et al. Early stroke treatment associated with better outcome. *Neurology*. 2000;55:1649–55.
- 90 IST-3 Collaborative Group. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. *Lancet*. 2012; 379:2352–63.
- 91 Emberson J, Lees K, Lyden P, Blackwell L, Albers G, Bluhmki E, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet*. 2014;384:1929–35.
- 92 Ingall T, O'Fallon W, Asplund K, Goldfrank LR, Hertzberg VS, Louis TA, et al. Findings from the reanalysis of the NINDS tissue plasminogen activator for acute ischemic stroke treatment trial. *Stroke*. 2004;35: 2418–24.
- 93 Kim J, Fonarow GC, Smith EE, Reeves MJ, Navalkhe DD, Grotta JC, et al. Treatment with TPA in the “golden hour” and the shape of the 4.5 hour time-benefit curve in the National US get with the guidelines-stroke population. *Circulation*. 2017;135: 128–39.
- 94 Morgenstern LB, Bartholomew LK, Grotta JC, Staub L, King M, Chan W. Sustained benefit of a community and professional intervention to increase acute stroke therapy. *Arch Intern Med*. 2003;163:2198–202.
- 95 Wojner-Alexandrov AW, Alexandrov AV, Rodrigues D, Persse D, Grotta JC. Houston paramedic and emergency stroke treatment and outcomes study (HoPSTO). *Stroke*. 2005;36:1512–8.
- 96 Alberts MJ. The stroke belt consortium. *J Stroke Cerebrovasc Dis*. 1996;6:54–8.
- 97 Morgenstern LB, Steffen-Batey L, Smith MA, Moyé LA. Barriers to acute stroke therapy and stroke prevention in Mexican Americans. *Stroke*. 2001;32:1360–4.
- 98 Kleindorfer D, Miller R, Sailor-Smith S, Moomaw CJ, Khoury J, Frankel M. The challenges of community-based research: the beauty shop stroke education project. *Stroke*. 2008;39:2331–5.
- 99 Alexandrov AV, Grotta JC. Arterial reocclusion in stroke patients treated with intravenous tissue plasminogen activator. *Neurology*. 2002;59:862–7.
- 100 Alexandrov AV, Molina CA, Grotta JC, Garami Z, Ford SR, Alvarez-Sabine J, et al.; CLOTBUST Investigators. Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke. *N Engl J Med*. 2004;351: 2170–8.
- 101 Deeds SI, Barreto A, Elm J, Derdeyn CP, Berry S, Khatri P, et al. The multiarm optimization of stroke thrombolysis phase 3 acute stroke randomized clinical trial: rationale and methods. *Int J Stroke*. 2020 Dec 9: 1747493020978345. Epub ahead of print.
- 102 Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. *Lancet*. 2000;355:1670–4.
- 103 Albers GW, Lansberg MG, Norbash AM, Tong DC, O'Brien MW, Woolfenden AR, et al. Yield of diffusion-weighted MRI for detection of potentially relevant findings in stroke patients. *Neurology*. 2000;54:1562–7.
- 104 Albers GW, Thijs VN, Wechsler L, Kemp S, Schlaug G, Skalabrini E, et al. Magnetic resonance imaging profiles predict clinical response to early reperfusion: the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study. *Ann Neurol*. 2006;60:508–17.
- 105 Baron JC, Boussier MG, Comar D, Soussaline F, Castaigne P. Noninvasive tomographic study of cerebral blood flow and oxygen metabolism in vivo. Potentials, limitations, and clinical applications in cerebral ischemic disorders. *Eur Neurol*. 1981;20: 273–84.
- 106 Baron JC, Macrae IM, Adams HP Jr, Dirnagl U. ESC-BRAIN: experimental and clinical stroke research – do they connect? Meeting report of the ESC-BRAIN joint symposium held in London and Shanghai in May 2013. *Cerebrovasc Dis*. 2013;36:306–21.
- 107 Lansberg MG, Cereda CW, Mlynash M, Mishra NK, Inoue M, Kemp S, et al. Response to endovascular reperfusion is not time-dependent in patients with salvageable tissue. *Neurology*. 2015;85:708–14.
- 108 Nambiar V, Sohn SI, Almekhlafi MA, Chang HW, Mishra S, Qazi E, et al. CTA collateral status and response to recanalization in patients with acute ischemic stroke. *Am J Neuroradiol*. 2014;35:884–90.
- 109 Walter S, Kostopoulou P, Haass A, Helwig S, Keller I, Licina T, et al. Bringing the hospital to the patient: first treatment of stroke patients at the emergency site. *PLoS One*. 2010;5:e13758.
- 110 Ebinger M, Winter B, Wendt M, Weber JE, Waldschmidt C, Rozanski M, et al. Effect of the use of ambulance-based thrombolysis on time to thrombolysis in acute ischemic stroke: a randomized clinical trial. *JAMA*. 2014;311:1622–31.
- 111 Parker S, Bowry R, Wu T, Noser E, Jackson K, Richardson L, et al. Establishing the first mobile stroke unit in the United States. *Stroke*. 2015;46:1384–91.
- 112 Wu TC, Parker SA, Jagolino A, Yamal JM, Bowry R, Thomas A, et al. Telemedicine can replace the neurologist on the mobile stroke unit. *Stroke*. 2017;48:493–6.
- 113 Bowry R, Parker SA, Yamal JM, Hwang H, Appana S, Rangel-Gutierrez N, et al. Time to decision and treatment with tPA (tissue-type plasminogen activator) using telemedicine versus an onboard neurologist on a mobile stroke unit. *Stroke*. 2018;49:1528–30.
- 114 Kunz A, Ebinger M, Geisler F, Rozanski M, Waldschmidt C, Weber JE, et al. Functional outcomes of pre-hospital thrombolysis in a mobile stroke treatment unit compared with conventional care: an observational registry study. *Lancet Neurol*. 2016;15: 1035–43.
- 115 Ebinger M, Siegerink B, Kunz A, Wendt M, Weber JE, Schwabauer E, et al. Association between dispatch of mobile stroke units and functional outcomes among patients with acute ischemic stroke in Berlin. *JAMA*. 2021;325:454–66.
- 116 Grotta JC, Yamal J-M, Parker SA, Rajan SS, Gonzales NR, Jones WJ, et al. Prospective, multicenter, controlled trial of mobile stroke units. *NEJM*. 2021;385:971–81.
- 117 Jolugbo P, Ariens RAS. Thrombus composition and efficacy of thrombolysis and thrombectomy in acute ischemic stroke. *Stroke*. 2021;52:1131–42.