Published in final edited form as:

N Engl J Med. 2016 March 03; 374(9): 809–811. doi:10.1056/NEJMp1514696.

Stroke and t-PA — Triggering New Paradigms of Care

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Stroke takes no prisoners. Every day, more than 14,000 people of all ages and ethnic backgrounds die from a stroke. According to the World Health Organization, stroke is the second leading cause of death among people over 60 years of age and the fifth leading cause among those 15 to 59 years of age. The annual number of deaths from stroke exceeds the number from AIDS, tuberculosis, and malaria combined, and it's the leading cause of long-term disability globally.

Today, stroke is seen as a medical emergency. Suspected stroke is prioritized in triage systems, public health campaigns promote public recognition of stroke onset, and health systems have been reconfigured to permit speedy access to stroke care. But this response is a recent phenomenon, dating, I would argue, to the 1995 publication of a research article by a National Institute of Neurological Disorders and Stroke (NINDS) study group on recombinant tissue plasminogen activator (t-PA).¹

It's rare to be able to date a shift in the conception and treatment of a condition to a particular moment. But the results of the NINDS trial marked a watershed in the history of stroke, since t-PA was the first proven therapy for acute stroke. Its success drove the reconceptualization of stroke as a medical emergency and made patients with stroke a priority of health systems for the first time. Today, stroke commands attention in public health agendas and policy initiatives worldwide. The recognition of the importance of this disorder could not have been anticipated as recently as the early 1990s.

Stroke has always been part of the medical landscape. Hippocrates described one-sided paralysis with associated loss of speech, calling it apoplexy. In the 17th century, Johann Wepfer suggested that apoplexy was caused by interference with cerebral blood flow, and throughout the 18th and 19th centuries, researchers studied the condition to explore relationships between lesions and brain function. In the mid-20th century, pioneers such as Canadian neurologist C. Miller Fisher built a new understanding of stroke through clinical and pathological studies. Fisher established that the incidence of thrombosis of the carotid artery was much higher than had been thought and that transient ischemic attacks were critical warning signs of stroke. Around the same time, new techniques such as angiography, cerebrovascular surgery, and anticoagulation began to be introduced.

In 1954, Fisher moved to Massachusetts General Hospital (MGH), where he and neurology chief Raymond Adams created the first stroke service.² The same year, the first Princeton Conference on cerebrovascular disease was held, chaired by Irving Wright, a vascular specialist who deplored the “fatalistic philosophy” that dogged medical attitudes toward stroke.³ He won support from philanthropist and health activist Mary Lasker, the American Heart Association (AHA), and the National Heart Institute. The event marked the beginning of a new approach to cerebrovascular disease. By November 1963, the AHA had established a stroke program, and stroke appeared on U.S. public health agendas in 1964, when, thanks in part to Lasker’s lobbying, President Lyndon Johnson established the Commission on Heart Disease, Cancer, and Stroke.²

But stroke remained a low priority in most places. Besides MGH, notable exceptions included Melbourne, Australia, where neurologist Peter Bladin built a dedicated stroke unit supported by research and was instrumental in setting up the Australian Stroke Society, and Sweden, where Per Olov Wester created such a unit, founded the Scandinavian Society for Cerebrovascular Diseases, and helped establish the Swedish National Quality Register for Stroke Care. Since 1998, the register has included data from all hospitals in Sweden that have admitted patients with acute stroke.

The creation of international networks of physicians treating stroke and stroke researchers facilitated the collection of data about incidence, mortality, and outcomes and improved knowledge of stroke epidemiology. By the early 1990s, there was strong evidence of the benefits of care in a stroke unit. Nevertheless, care remained fragmented among various specialties and organizational structures, and physicians struggled to gain recognition and resources for stroke.

The potential of thrombolytic agents for treating ischemic stroke was recognized at least as early as the 1950s, but the high risk of death from intracranial hemorrhage precluded much experimentation. The stroke community expected that t-PA trials in the early 1990s would merely confirm previous evidence that the risks exceeded the benefits. Indeed, the international research agenda was focused on initiatives such as the development of neuroprotective drugs. But the NINDS trial differed from earlier studies: because research had suggested that stroke was a process rather than an event and that time was therefore a critical element, investigators were paying attention to the time from stroke onset to t-PA administration.

The findings of the NINDS trial established t-PA as efficacious within a 3-hour time frame, with improvements in functional outcomes at 3 months. The greatest improvements were seen when t-PA was administered within 90 minutes after stroke onset, and there was no significant increase in mortality among patients receiving t-PA, despite a 6% increase in absolute risk of intracerebral hemorrhage. Health systems rapidly adopted t-PA as a new standard of care, in the context of economic evidence that early treatment would produce long-term financial savings. Neurologists delighted in the new treatment possibilities.

The quality of the NINDS data, however, was challenged by emergency physicians, who argued that the results of a single small study could not be extrapolated to all patients and

that the evidence was insufficient to establish a clear benefit.⁴ But a 2004 reevaluation of the NINDS data reconfirmed the original claims, and a 2014 meta-analysis presented at the American Stroke Association's international conference showed that t-PA significantly improved outcomes regardless of a patient's age or stroke severity. Yet skeptics continue to challenge the reliability of the evidence, most recently that from the third International Stroke Trial published in 2012.

Notably, t-PA is not a universally administered therapy; it is given only to 5 to 10% of patients with acute stroke, owing to strict clinical criteria for use, patients' delayed presentation at emergency departments, and continuing uncertainties about risks and benefits.⁵ Yet in locales where services have been reconfigured (through centralization or telemedicine) to meet the t-PA time frame, outcomes have improved measurably for all patients with stroke, not just those given t-PA.⁵ These improvements have been achieved because t-PA led to the prioritization of stroke in health systems and policy, facilitating the establishment of stroke units and wider implementation of drug interventions (e.g., aspirin and anticoagulants), swallow tests, and rapid progression to rehabilitation support — all of which were supported by sound evidence before 1995.

Thus, the decisive benefit of t-PA was the establishment of new treatment paradigms requiring patients with stroke to obtain specialized care as quickly as possible. Clinicians and health systems have had to adopt a multifaceted, integrated approach to conform to this model, which is realized through the creation of a stroke infrastructure, and that infrastructure has produced indirect benefits for all patients with stroke. The most important innovation since t-PA is endovascular therapy, whose benefits have been proven in recent trials. Like t-PA, endovascular therapy is suitable only for a minority of patients, requires rapid access to specialist care, and promises to drive a new raft of service developments.

Despite the effect on the care and outcomes of stroke realized by the introduction of t-PA, at some level, responses to the condition continue to be shaped by its longer history of neglect. Attempts to brand strokes as “brain attacks” demanding the same public prominence as “heart attacks” have largely failed. And the priority now accorded to acute care for stroke contrasts with the limited emphasis still given to longer-term rehabilitation after stroke and public health policies aimed at preventing it — a contrast that illuminates a persistent bias toward procedure-oriented medicine. Nevertheless, the lessons of stroke's history should encourage us to consider carefully whether clinicians and health systems are doing what the evidence indicates is therapeutic for other conditions that are currently accorded low priority.

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