

# Management of Acute Stroke: Impact of Registration Studies

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## Abstract-

Stroke is a life-threatening or life-changing disease that is expensive in health care costs and lost productivity. Stroke also is a leading cause of human suffering. While the risk of stroke may be reduced with advances in prevention, recent advances in acute care can limit the consequences of stroke. In particular, the success of reperfusion therapies including intra-arterial interventions and intravenous administration of thrombolytic agents means that some patients with stroke may be cured.

Still, the time window for effective treatment of stroke is relatively short. As a result, modern stroke management requires the close collaboration of the public, health care providers, administrators, insurance companies, and the government. Potential strategies to extend modern stroke care to as many patients as possible include 1) educational programs to train community emergency medical service personnel and physicians, 2) development of stroke care plans at community hospitals, 3) an integrated community-comprehensive stroke center program based on consultation, and telemedicine. The goal is to have a highly integrated approach to provide emergency treatment of the stroke that provides key emergency treatment, including intravenous administration of thrombolytic medications, at a community hospital (primary stroke center) with evacuation to a comprehensive stroke center that has resources and expertise that are not available in the primary stroke center. Taiwan is an ideal location for the development of such regional stroke programs.

**Key Words:** acute ischemic stroke, comprehensive stroke centers, emergency treatment, thrombolytic therapy

*Acta Neurol Taiwan 2010;19:153-163*

Stroke is a leading cause of death and disability in Taiwan. A recent study based on the National Health Insurance Research Database reported that more than 250,000 Taiwanese were hospitalized for stroke during the time period 1998-2007<sup>(1)</sup>. In the United States, approximately 750,000 new or recurrent strokes occur annually and stroke accounts for approximately 5% of

deaths<sup>(2)</sup>. Besides being a leading cause of death, disability, and human suffering, the economic consequences of stroke also are considerable. The estimated annual health costs from stroke are approximately US\$ 80 billion<sup>(2)</sup>. In 1996, Taylor et al.<sup>(3)</sup> calculated that the life-time, per-patient cost of ischemic stroke was more than US\$ 90,000. The per-patient costs for both intra-

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Received & Accepted July 2, 2010.

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cerebral and subarachnoid hemorrhages are even higher. The economic costs are direct and indirect. The direct costs of management of cerebrovascular disease include measures to prevent stroke (treatment of risk factors, antithrombotic medications, surgical procedures,) interventions to treat acute stroke (specific stroke treatment such as thrombolytic therapy and therapies to prevent or control complications,) and measures to maximize recovery after stroke (rehabilitation.) The indirect costs of stroke include loss of productivity because the patient or family care givers may not be able to work and disability or social service payments.

In the past, patients and families approached stroke with a sense of hopelessness. Their opinions were matched by that of health care providers who had a sense of helplessness. Nothing had been established as effective as improving outcomes and as a result, there was no sense of urgency in diagnosis and treatment. This sense of stroke was summarized by the term cerebrovascular accident (CVA.) However, there is nothing accidental about stroke and the term CVA should be abandoned.

A number of advances in the diagnosis and treatment of patients with cerebrovascular disease have occurred in the last 40 years; these changes are improving all components of care including emergency management. In the early 1970's, computed tomography (CT) allowed for early and accurate differentiation of hemorrhagic from ischemic stroke. In the same decade, a Canadian study demonstrated that aspirin was effective in lowering the risk of stroke among high-risk persons<sup>(4)</sup>. This finding was confirmed by numerous subsequent reports and led to development of new antiplatelet agents such as ticlopidine, clopidogrel, and the combination of aspirin and extended-release dipyridamole that are widely used to prevent stroke<sup>(5)</sup>. In the 1980's, nimodipine was shown to be effective in lowering the risk of brain ischemia after aneurysmal subarachnoid hemorrhage<sup>(6)</sup>. This was the first intervention to achieve regulatory approval for treatment of any form of acute stroke. The subsequent development of magnetic resonance imaging (MRI) greatly improved the evaluation of patients with stroke, for example, it allows for early detection of ischemic stroke (diffusion weighted imaging,) discovery of abnor-

mal perfusion, and examination of the underlying vascular anatomy (magnetic resonance angiography.) These advances also have stimulated new techniques in CT vascular imaging and perfusion. The advent of transesophageal echocardiography improved the cardiac evaluation of patients with stroke.

In parallel with the advances in medical research, professional and public interest bodies authored statements to improve implementation of useful therapies in an attempt to provide cost-effective stroke care. Audiences for the guidelines vary and include physicians of multiple specialties, emergency medical services personnel, other health care professionals, administrators and governmental regulators, insurance companies, and the public. The statements are written by panels of experts including physicians and other health care professionals. The guidelines are adapted to the needs of the local community or region of the world. Some groups, such as the American Heart Association, have developed a series of focused, specific statements, while others such as the European Stroke Initiative, have created a single comprehensive document that covers all components of stroke care.<sup>(5,7-12)</sup> These statements include recommendations that discourage the use of diagnostic studies that are not sensitive or specific while advising the ordering of those tests that are useful. Similarly, the guidelines include recommendations that discourage the prescription of ineffective or unsafe therapies while promoting the use of therapies that are efficacious. Still, much of the management of acute ischemic stroke has not been tested by clinical trials and as a result, many of the components of guidelines for acute treatment are based on the consensus of experts and opinion leaders.

In the last 10 years, numerous clinical series and studies reported on the utility of intra-arterial therapies to treat ischemic stroke. Both mechanical and pharmacological interventions have been used. Some devices have been approved for treatment of acute arterial occlusions<sup>(13-17)</sup>. On the other hand, a number of interventions have been tested with negative results. Among the therapies that have not been shown to be effective include a large number of neuroprotective agents, early administration of anticoagulants, surgical evacuation of

hematomas located deeply in the cerebral hemispheres, and early administration of recombinant Factor VII a for treatment of cerebral hemorrhage. The most important advance in treatment, which has revolutionized the treatment of stroke, is the discovery that early intravenous administration of recombinant tissue plasminogen activator (rt-PA) is effective in improving outcomes when administered within the first 3-4.5 hours after stroke.<sup>(18,19)</sup> This discovery is the engine that is driving the current strategy to acute stroke care. The goal of increasing the likelihood that more patients could receive treatment with rt-PA has prompted the development of regional, national and continental guidelines that provide information to physicians and other health care providers. While local interpretation of the data and different requirements may vary among countries, governmental regulatory bodies have approved the use of therapies, including intravenous rt-PA, for treatment of acute stroke. Both the United States and Taiwan have approved the use of rtPA for the treatment of persons with ischemic stroke.

### **Brain attack**

The current approach to the treatment of patients with acute ischemic stroke is summarized by the term “brain attack.” The use of brain attack to describe stroke is an obvious adaptation of the term “heart attack” for acute myocardial ischemia. It is used to increase the sense of urgency for both the public and the health care system. Much of the management of acute myocardial ischemia and acute cerebral ischemia is similar. Both are acute diseases due to thromboembolic arterial occlusions and both are associated with serious complications. Definitive treatment of both conditions emphasizes emergency measures to restore arterial perfusion through the use of thrombolytic agents or endovascular interventions. A chain of survival for persons with ischemic stroke has been identified<sup>(20)</sup>. (Table 1) Rapid movement of a patient through these steps allows for early treatment of stroke and gives the potential for improved outcome. The chain of survival involves the collaboration of the public, emergency medical services, hospitals, emergency departments, physicians, and other health professionals. A team effort is needed for a successful

**Table 1.** Chain of Survival Treatment of Acute Ischemic Stroke

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Public:
Prompt recognition of the symptoms and signs of stroke by patient or observers
Public educational programs for general public and high-risk persons
Know the correct response to the appearance of symptoms and signs of stroke
Call emergency medical services, or
Go immediately to a hospital emergency department
Emergency medical services:
Dispatcher recognizes symptoms and signs of stroke
Prompt dispatch of ambulance and paramedics
Rapid evaluation in the field
Speedy transport to the closest hospital with stroke expertise (primary stroke center)
Bypass a hospital that does not have an acute stroke protocol
Emergency department:
Have identified acute stroke care team
Have a pre-planned protocol to treat acute stroke
Rapid clinical and laboratory evaluation
Confirm diagnosis of ischemic stroke
Screen for contraindications for thrombolytic therapy
Administer thrombolytic therapy
Transfer to a comprehensive stroke center

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outcome.

### **Regional stroke programs**

The integration of a central comprehensive stroke center and satellite primary stroke centers is another component of the strategy to increase the number of patients that may be treated within the first hours after stroke. The precise organization of the regional program is based on the nature of the geographical region and the norms of the community. The program links the public, emergency medical services, and governmental bodies to the primary and comprehensive stroke centers. One of the goals is development of protocols and tactics that address any potential bottleneck to the rapid evaluation and treatment of persons with stroke. Another goal is to

develop a coordinated strategy that may be implemented by all health care providers. The general organization of a regional stroke program would be a hub-and-spoke system similar to that used by airlines where a major airport serves as the central location for flights coming from or going to smaller cities. In this circumstance, the comprehensive stroke center situated in a major hospital coordinates treatment with the smaller, peripheral community hospitals that are located in the same geographic region. The distances between the primary and comprehensive stroke may affect plans for rapid land or air evacuation of the patient. The initial emergency treatment would be at the community hospital. This component of management may occur with or without consultation from vascular specialists at the comprehensive center. The communication could be via telephone or telemedicine. Teleradiology to permit immediate interpretation of scans could be included.

Telemedicine also has been used successfully to speed the treatment of patients with stroke.<sup>(21-26)</sup> Telemedicine is an alternative to telephone consultation and may help with the goal of speeding evaluation and treatment of patients in remote locations or small hospitals. The utility of this technology was reviewed and the American Heart Association authored a position paper that includes recommendations on the use of telemedicine in emergency stroke care<sup>(27,28)</sup>. Both emergency medicine physicians and vascular neurologists have positive attitudes towards the use of telemedicine in this setting.<sup>(29)</sup> The advantages of telemedicine are considerable. It allows the vascular neurologist to directly assess the patient and to directly examine the brain imaging study. This may augment decision making and early treatment. For example, Capampangan et al.<sup>(30)</sup> concluded that telemedicine was superior to telephone consultation in determining eligibility for treatment with rtPA. Besides speeding treatment of patients with rtPA, telemedicine may be used to augment recruitment of patients into clinical trials<sup>(31)</sup>. On the other hand, telemedicine is expensive to purchase and maintain. Among the costs are the charges for computers or robots at both the central hospital and the local institutions as well as communication charges. Because this is an evolving field, the

technology becomes out-of-date relatively rapidly. The cost-effectiveness of the system may be questioned if it is used only for stroke. As a result, the use of telemedicine probably would need to be expanded to include other medical emergencies such as severe trauma or myocardial infarction in order for the system to be financially viable. Still, the integration of telemedicine into a regional stroke program has been successful. For example, Pervez et al.<sup>(32)</sup> reported on the experience of a large medical center in Massachusetts. Patients in community hospitals were treated with the assistance of either telephone or telemedicine consultation and then evacuated to the major medical center; 115 patients were treated at the comprehensive center while 181 patients were treated at outside hospitals. Outcomes (rates of hemorrhage, mortality, length of stay, and status at discharge) were similar among patients treated in the community setting and at the major medical center.

### ***Primary stroke centers***

Despite advances in stroke research and regulatory approval, the implementation of modern stroke therapy on a community setting has been slow. Kleindorfer et al.<sup>(33)</sup> reviewed the Medicare claims in 4750 hospitals in the United States during 2005-2007. During that time nearly 500,000 patients aged 65 or older with ischemic stroke were treated. Ten years after the approval of rt-PA, approximately 64% of American hospitals had not treated a single patient during the 2-year period. Less than 1% of hospitals treated 10 or more cases during the same time. Small or rural hospitals were those least likely to treat patients with rt-PA. Thus, despite having a therapy of proven efficacy for more than one decade, rt-PA is underutilized. Hence, there is a need to increase the frequency of administration of rt-PA and other therapies of proven utility in order to improve outcomes after stroke. In response, the American Heart Association developed the "Get with the Guidelines" program to facilitate implementation of the guidelines and to improve the quality of care of persons with acute stroke. The program includes educational programs for physicians and other health care professionals and data collection materials. The program also is linked with reimbursement to

providers by insurance companies and the government.

The value of the “Get with the Guidelines” program has been evaluated. Twelve measures of stroke care were assessed by looking at the treatment of 18,410 patients with transient ischemic stroke (TIA) or ischemic stroke at 99 community or academic hospitals in the United States<sup>(34)</sup>. Data collected before and after the implementation of the program were compared; improvements in care were considerable<sup>(35)</sup>. For example, the use of thrombolytic medications among persons first seen within 2 hours of ischemic stroke increased from 23.5% to 40.8% ( $p < .001$ ) and use of lipid-lowering medications among persons with elevated cholesterol increased from 58.7% to 77% ( $p < .001$ .) In another report, Schwamm et al.<sup>(36)</sup> reported on the effects of the implementation of the program during 2003 - 2007. The study involved more than 320,000 patients with TIA or ischemic stroke seen at 790 hospitals. The composite of the twelve indicators of quality stroke care improved from 83.5% to 94% ( $p < .0001$ .) Recently, Saver et al.<sup>(37)</sup> found that thrombolytic therapy was administered to 27% of patients arriving within 1 hour of stroke onset when they arrived at a hospital involved in the Get with the Guidelines program. These experiences show that a coordinated educational program that emphasizes compliance with the guidelines results in improved patient management.

Complementing the “Get with the Guidelines” program is a nationwide program across the United States that leads to the designation of hospitals as a Primary Stroke Center by the Joint Commission, the organization that certifies hospitals. (Table 2) In complementary programs, several state health departments have programs to promote development of primary stroke centers. Both the Joint Commission and the state certification programs are aimed mainly at smaller community hospitals. Both the Joint Commission and the state programs involve an institutional application, external review, certification, collection of quality data, and recertification.

Because of geography or other factors, many patients with stroke are not able to reach a larger, comprehensive stroke center in sufficient time to have their vascular event treated within the current time windows. Thus, the mission of the primary stroke center is to pro-

**Table 2.** Activities of a Primary Stroke Center

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An emergency stroke team available 24 hours/day, 7 days/week
Physicians, other health care professionals
Presence of a protocol for emergency evaluation and treatment
Focuses on treatment in emergency department
Perform a rapid evaluation — expedited by pre-printed orders
Differentiate hemorrhagic from ischemic stroke
Exclude other causes of neurological symptoms
Screen for contraindications for treatment
Look for serious acute complications of stroke
Assess severity of stroke using NIH Stroke Scale
Complete entire evaluation within 1 hour of arrival
Emergency treatment of ischemic stroke
Intravenous administration of rtPA
Have telephone or electronic contact with comprehensive stroke center
Have a policy for transfer patients to comprehensive stroke center

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vide emergency management of these patients. Components of acute management include general emergency care, treatment of acute complications of stroke, and treatment of the acute ischemic stroke itself<sup>(38,39)</sup>. The primary stroke center would be a local focus for treatment. Ambulances and emergency services would bypass those hospitals that are not designated as primary stroke centers because going to an institution that does not have a stroke plan delays treatment. At the primary stroke center, patients with acute stroke should be triaged as having the highest priority similar to those persons with acute myocardial infarction. Institutions would have clinical and laboratory services available on a 24 hour/day and 7 day/week basis. This requirement includes brain imaging (CT) with physician interpretation. The aim is to have treatment of eligible patients with rtPA within 1 hour of arrival in the emergency department. To implement the program, hospitals with a primary stroke center designation designate a group of physicians and allied professionals combined into an

acute stroke care team, written policies on the emergency evaluation and treatment of stroke, and a written agreement of collaboration with a comprehensive stroke center. Because most of the primary stroke centers do not have neurologists available in person, the availability of telephone consultation or telemedicine could be used to expedite care. The emergency department would have a supply of rtPA available for immediate use. Because primary stroke centers may not have the full range of resources or expertise available for overall management of stroke, the goal is to transfer patients to a comprehensive stroke center for subsequent specialized management after the initial emergency care, including treatment with rtPA. The concept of early treatment with rtPA at the local hospital and then transfer to the larger specialized hospital is summarized in the term “drip and ship.”

### ***Comprehensive stroke centers***

A comprehensive stroke center is a larger tertiary level institution that is the core resource for the regional stroke program. It has physicians with special expertise in stroke such as vascular neurologists, vascular surgeons, neurointerventional physicians, neurosurgeons, and intensive care specialists<sup>(40)</sup>. (Table 3) In addition, the comprehensive stroke center has resources such as an intensive care unit or stroke unit that allows for specialized nursing care and the use of stroke-specific care maps. The institution also has a multidisciplinary stroke team that includes physicians, nurses, rehabilitation specialists, and social services that provides integrated management. The patient care-related components are complemented by stroke educational and research programs.

While the comprehensive stroke center has the same emergency services and requirements as the primary stroke centers, its primary role often is complementary in that it is receiving patients treated and sent from smaller outlying centers. The concentration of resources and expertise allows patients to receive state-of-the-art stroke care by providing services that are not available in smaller hospitals. This complementary approach is a cost-effective strategy in that it avoids the duplication of expensive technologies and expensive medical services.

**Table 3.** *Activities of a Comprehensive Stroke Center*

Duties
Function as a primary stroke center
Provide overall leadership for a regional stroke program
Develop care protocols for all hospitals in region
Develop public educational programs for region
Develop professional educational programs for region
Availability for emergency consultation and referral
Organize and coordinate clinical research studies
Advocate for stroke and patients with stroke
Components
Physicians
Vascular neurologists
Neurosurgeons
Vascular surgeons
Neurointerventional physicians
Neurorehabilitation physicians
Neuroradiologists
Neurointensive care specialists
Other health care professionals
Nurses
Rehabilitation specialists
Stroke coordinator
Resources
Stroke unit (and/or intensive care unit)
Modern brain imaging
Modern vascular and cardiac imaging
Neurointerventional facility
Operating rooms
Rehabilitation
Other components
Stroke educational programs
Clinical stroke research programs

The leadership of the comprehensive stroke center is by physicians who have special expertise and experience in stroke care; in most cases, the director is a neurologist. In the United States, the American Board of Psychiatry and Neurology (ABPN) developed the subspecialty of vascular neurology, which recognizes the special and distinct body of knowledge that comprises stroke<sup>(41)</sup>. The certification of vascular neurologists has

stimulated the development of fellowship programs that involve a minimum of one year of additional training in stroke that follows completion of a neurology residency. Given the rapid changes in knowledge about stroke, the certificate issued by the ABPN is valid for 10 years; a formal re-certification process is in place. The presence of a physician leader in stroke is a crucial component of a comprehensive stroke center.

Similarly, a stroke unit is a core resource. The definition of a stroke unit varies. Some stroke units include an intensive care component that involves monitoring and critical care. Other stroke units include a rehabilitation component. Still, most stroke units have a geographically defined facility. It is staffed by physicians, nurses, rehabilitation specialists, and other health professionals who have special expertise in the diagnosis and treatment of persons with stroke. This concentration eases communications and increases close interactions. The development of predefined stroke protocols and care maps allows for efficient and effective management of patients<sup>(42,43)</sup>. Outcomes among persons admitted to stroke units are superior to those found among patients admitted to general medical wards<sup>(44,45)</sup>. Mortality is reduced and the likelihood of being independent is increased. One of the important advantages of stroke units is that this coordinated management may be prescribed to a wide range of patients with stroke including those who could not be treated with rtPA because they arrived too late to receive the medication or because they had contraindications for treatment. The stroke unit also provides the opportunity for physicians of a wide variety of specialties to be involved in the treatment of stroke.

The leadership of the comprehensive stroke center also should be available to give guidance and support to the primary stroke centers in the region including being on call for emergency consultation. They should develop care protocols that may be used in both the comprehensive center and the satellite primary centers. These protocols are developed for the emergency and in-hospital management of persons with either ischemic or hemorrhagic stroke. While the emphasis should be on emergency management, the protocols should include the full spectrum of treatment of patients with stroke including

prevention, rehabilitation, and return to society. The comprehensive stroke center also could develop a local public educational program that is to be aimed at the needs of the region. The message should be simple and clear. This may be adapted from national or other programs but should be tailored to meet the cultural and societal needs of the persons in the region. The public should be educated about the clinical features of stroke and TIA and they should be informed about the correct response, which is to seek medical care immediately. The public programs could involve lectures, posters, flyers, television or radio advertising, and billboards. The public educational programs are complemented by professional educational programs aimed at community physicians, hospital personnel, and emergency medical services personnel. These educational initiatives may take the form of lectures, seminars, computer-based programs, or printed materials. Because of the rapidly evolving nature of stroke, updates are important.

The leadership of the comprehensive stroke center also could initiate and coordinate clinical research studies. The opportunities for research in stroke are vast. Many of the recommendations in the current stroke guidelines are based on consensus or opinion, the future availability of data likely will modify the recommendations. In addition, the leadership of the comprehensive stroke center may serve as advocates for both stroke and stroke patients. The advocacy would be for more funding of care, improved resources for patients with stroke, increased support for stroke-related research, and increased public educational programs. The audiences vary but include governmental officials and administrators, public health administrators, hospital directors, and the public. In Taiwan, the emphasis of these advocacy programs would be on the importance of stroke as a public health problem and the opportunities to improve care for more persons with stroke. In addition, the real progress in stroke care that has occurred in the last 30 years should be emphasized along with a plea to continue the efforts to improve care. While stroke care is much better than in the past, there still is considerable room for improvement.

## CONCLUSION

Stroke remains a life-threatening or life-changing disease that is expensive both in terms of health care costs and in human suffering. Management of patients with cerebrovascular disease is advancing. Effective medical therapies and surgical interventions are available to lower the risk of stroke. Stroke can be prevented but the therapies must be started in a timely manner, particularly in high-risk persons such as those with TIA. The consequences of acute ischemic stroke can be limited by early prescription of therapies of proven utility such as intravenous administration of rtPA. Some patients with stroke can be cured. In other cases, the neurological injury may be lessened. However, such success requires the close collaboration of the public, a wide range of health care professionals, hospitals and their administrators, and the government. Advances in stroke care in Taiwan will continue. However, regardless of future improvements in stroke, success will be linked to early treatment. Time truly is brain.

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