Evolving Treatments for Acute Ischemic Stroke

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Abstract: The purpose of this article is to review advances in stroke treatment in the hyperacute period. With recent evolutions of technology in the fields of imaging, thrombectomy devices, and emergency room workflow management, as well as improvement in statistical methods and study design, there have been groundbreaking changes in the treatment of acute ischemic stroke. We describe how stroke presents as a clinical syndrome and how imaging as the most important biomarker will help differentiate between stroke subtypes and treatment eligibility. The evolution of hyperacute treatment has led to the current standard of care: intravenous thrombolysis with tissue-type plasminogen activator and endovascular treatment for proximal vessel occlusion in the anterior cerebral circulation. All patients with acute ischemic stroke are in need of hyperacute secondary prevention because the risk of recurrence is highest closest to the index event. The dominant themes of modern stroke care are the use of neurovascular imaging and speed of diagnosis and treatment. (Circ Res. 2016;118:1425-1442. DOI: 10.1161/CIRCRESAHA.116.307005.)

Key Words: biomarker ■ ischemic stroke ■ secondary prevention ■ standard of care ■ stroke ■ thrombectomy ■ thrombolysis

Introduction: Stroke Is a Syndrome

Stroke is defined as a sudden loss of neurological function because of a vascular cause. Broadly, stroke is divided into ischemic (≈85%) and hemorrhagic types (≈15%). Ischemia may be caused by large or small artery occlusions both intracranial and extracranial. Arterial occlusions may be caused by embolic (cardioembolic and arteroembolic), atherosclerotic, traumatic, inflammatory, infectious, or degenerative mechanisms. Spontaneous hemorrhagic stroke can be divided into parenchymal hemorrhage and subarachnoid hemorrhage with the latter most commonly associated with ruptured intracranial aneurysms. The least common variety of stroke is venous infarction because of cerebral venous thrombosis, which may have protean manifestations including both hemorrhage and necrotic cell death.1 The key principle of stroke nosology is that stroke is a syndrome with multiple possible causes and a wide range of symptomatic presentations from mild and transient to devastating and fatal.

The continuum of the ischemic stroke syndrome has traditionally been defined by the duration of symptoms and signs. This in turn is related to the length of time that a vessel is occluded or the neurovascular bed is affected by ischemia. The brain is dependent on an adequate blood supply to bring oxygen and nutrients as well as remove metabolic waste to maintain neuronal functioning; when the cerebral blood flow ceases neuronal damage and necrosis can occur in specific neurovascular...
The dominant mechanisms of brain ischemia include small vessel disease, artery-to-artery thromboembolism (arteroembolism), cardioembolism, and occlusive arterial disease because of atherosclerosis and arteriosclerosis. The cause of ischemia is important for the secondary prevention of strokes and in a cruder way influences choices for acute treatment. In the acute setting, the clinician does not have access to detailed information on stroke mechanism in many instances, and the treatment of all ischemic strokes that are potentially disabling is somewhat uniform. This treatment is dependent on removing the occlusion from large or small arteries, either by intravenous administration of fibrinolytic agents such as recombinant tissue-type plasminogen activator (rt-PA) or by endovascular intervention. Because endovascular techniques are applicable only to large vessel occlusions, it has become important to identify which vessel is occluded and where the occlusion is located through the use of reliable imaging biomarkers.

This article will review the evolving treatments for acute ischemia in the first 24 hours post stroke including hyperacute secondary prevention because stroke is still the second most common cause of death worldwide and the third most common cause of disability. A large proportion of stroke survivors require long-term rehabilitation and extended nursing care. Long-term manifestations of stroke can include depression, post stroke fatigue, spasticity, and general loss of function. Although we have seen advances in stroke rehabilitation, it is hoped that burden of stroke can be reduced by preventing ischemic tissue death by treating stroke in the hyperacute period.

### Imaging as a Biomarker

In the absence of a physiological or blood biomarker, similar to serum troponin or the ECG for acute coronary syndromes, imaging has evolved as the biomarker for acute stroke. Initially, imaging in the clinical context of stroke was used to simply distinguish between ischemic and hemorrhagic strokes, and thus aid in decision making for the use of intravenous thrombolytic therapy. Imaging has now evolved such that its use in the hyperacute setting can elucidate stroke pathophysiology and provide critical diagnostic information that affects acute and individualized treatment decisions. The advancement in neurovascular imaging during the past 3 decades is the single most important factor in the development of stroke therapeutics.

### Computed Tomography

Noncontrast computed tomography (NCCT) remains the primary imaging modality for stroke syndrome presentations because of its fast acquisition and widespread availability. It can quickly differentiate between ischemic and hemorrhagic stroke but can also be used to quantify the extent of early ischemic changes (EICs). The Alberta Stroke Program Early CT Score (ASPECTS) was developed to provide a reliable, reproducible grading system assessing EIC in patients with anterior circulation ischemic strokes (www.aspectsinstroke.com). When grading ASPECTS, a 10-point scale is used; 10 prespecified regions are observed, and 1 point is subtracted for each region with parenchymal hypointenation (Figure 1). There is modest inter-rater reliability for the scoring of individual ASPECTS regions, as these are affected by training, experience, and scan quality. Despite this, the overall score has high reproducibility when dichotomized (ASPECTS 8–10 versus ASPECTS 0–7). For major ischemic stroke, ASPECTS has been validated against DW-MRI. Areas of hypointenation, representing EIC on NCCT are analogous to regions of low apparent diffusion coefficient on MR-DWI. Importantly, MR-DWI has greater sensitivity for regions of ischemia. Because of this disparity in sensitivity, the total score is 1 ASPECT point less on DW-MRI then NCCT on average for major ischemic stroke.

The difference between MR-DWI and NCCT sensitivity in minor ischemic stroke is such that low-volume lesions may only be identifiable on DW-MRI. Thus, a normal NCCT cannot rule out a minor stroke; as a corollary, NCCT has a low negative predictive value for small volumes of ischemia. The major role of NCCT in the setting of minor stroke is to exclude other possible cause of acute neurological symptoms such as brain tumors, subdural hemorrhage, or other space occupying lesions in the presence of which thrombolysis would be contraindicated.

### Table: Nonstandard Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>ASPECTS</td>
<td>Alberta Stroke Program Early Computed Tomography Score</td>
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<td>CAS</td>
<td>carotid artery stenting</td>
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<td>CHANCE</td>
<td>Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events</td>
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<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>CTA</td>
<td>computed tomographic angiography</td>
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<td>DW-MRI</td>
<td>diffusion-weighted magnetic resonance imaging</td>
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<td>ECASS (II)</td>
<td>European Cooperative Acute Stroke Study (II)</td>
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<tr>
<td>EIC</td>
<td>early ischemic changes</td>
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<tr>
<td>ICH</td>
<td>intracerebral hemorrhage</td>
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<td>IMS</td>
<td>Interventional Management of Stroke</td>
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<td>MCA</td>
<td>middle cerebral artery</td>
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<td>mRS</td>
<td>modified Rankin Scale</td>
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<td>NCCT</td>
<td>noncontrast computed tomography</td>
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<td>NIHSS</td>
<td>National Institutes of Health Stroke Scale</td>
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<td>NINDS</td>
<td>National Institute of Neurological Disorders</td>
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<td>OR</td>
<td>odds ratio</td>
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<tr>
<td>rt-PA</td>
<td>recombinant tissue-type plasminogen activator</td>
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<td>TIA</td>
<td>transient ischemic attack</td>
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Secondary prevention because stroke is still the second most common cause of death worldwide and the third most common cause of disability. A large proportion of stroke survivors require long-term rehabilitation and extended nursing care. Long-term manifestations of stroke can include depression, post stroke fatigue, spasticity, and general loss of function. Although we have seen advances in stroke rehabilitation, it is hoped that burden of stroke can be reduced by preventing ischemic tissue death by treating stroke in the hyperacute period.

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NCCT can be reliably used for clinical decision making as well as prognostication when standardized image quality and training are applied to detect EIC. In the acute setting, for example, lower ASPECTS scores can predict poor functional outcome after therapy; scores of \( \leq 7 \) are associated with an increased risk for thrombolysis-related parenchymal hemorrhage after intravenous thrombolysis alone or in combination with endovascular treatment. At present, there are no convincing data that the beneficial effect of thrombolysis can be predicted by ASPECTS score. Sulcal effacement without hypoattenuation and hence preserved gray-white delineation is visualized uncommonly in patients with stroke. Typically, it is associated with proximal vessel occlusion strokes associated with robust leptomeningeal collaterals preserving the underlying parenchyma. In contrast to clear hypoattenuation, this is not a sign of irreversible tissue injury but instead a sign that the tissue is potentially salvageable. Isolated sulcal effacement should not exclude patients from acute treatment with either intravenous thrombolysis or mechanical thrombectomy.

In the nonacute setting, NCCT can be used to help guide investigations by providing important clues to stroke cause. Old wedge-shaped cortical infarcts are suggestive for an embolic origin from a distal (if only present in one vascular territory) or a proximal source (if presents in multiple vascular territories). Periventricular white matter changes or lacunes might be suggestive of small vessel disease. When considered together as radiological expressions of small vessel disease, presence and severity of severe leukoaraiosis and lacunes on NCCT are associated with poor clinical outcomes in patients treated with intravenous thrombolysis. However, intravenous thrombolysis should not be withheld based on evidence of small vessel disease. In the subacute phase, further investigations can, therefore, be tailored in an effort to improve secondary stroke prevention and provide more accurate prognostication.

**Computed Tomographic Angiography**

Developments in computed tomographic angiography (CTA) imaging have now made it possible to routinely image blood vessels and furthered the evolution of acute stroke therapy. All of the recently published successful endovascular stroke trials (reviewed below) used CTA to select patients with proximal occlusions of their anterior circulation as target lesions for endovascular treatment (Figure 2A). The anatomy of the aortic arch, tortuosity of extracranial vessels, status of ipsilateral carotid bifurcation, and caliber of the left common carotid artery with a normal bifurcation, suggesting an easy access for intervention.
Willisian collaterals, and site and size of thrombus on CTA help the neurointerventionist plan the endovascular treatment approach, including choice of appropriate catheters. The quality of collateral assessment depends on the timing of image acquisition in relation to the intravenous contrast bolus. Assessment of collaterals is important as patients with robust pial vessel filling (good collaterals) generally have a small core, whereas patients with poor pial vessel filling (poor collaterals) are more likely to have large baseline infarct core. Moreover, independent of age, vessel occlusion and time, among patients with comparable ischemic burden, changes in collateral grade alone are associated with significant differences in initial stroke severity as well as clinical outcomes after endovascular therapy.

There is a strong correlation between collateral status on CTA and ASPECTS score as a measure for the brain parenchyma. Parenchymal perfusion can also be estimated through the use of CTA source images. These postcontrast whole-brain perfused blood volume axial source images are obtained by continuing to scan above the circle of Willis. Areas with a critical drop in cerebral blood volume seem hypodense. CTA source images ASPECTS may more accurately identify the volume of tissue that will ultimately infarct compared with NCCT alone (Figure 3).

Another new development in the assessment of collaterals has been the multiphase CT angiogram. The multiphase CT angiogram generates time-resolved images of pial arteries by triggering the first scan in late arterial phase based on bolus-monitoring and acquiring 2 subsequent scans without additional contrast in mid venous and late venous phase, ≈5 to 8 s apart. With 2 additional phases, abnormal backfilling pial arteries and collateral status can potentially be assessed, making collateral assessment less vulnerable to issues related to contrast-bolus timing. Key advantages of multiphase CT angiogram include speed, resistance to image degradation from patient motion, minimal additional radiation, no additional contrast material, whole-brain coverage, no requirement for postprocessing, and high interrater reliability. Asymmetries in collateral filling can guide intracranial occlusion assessment (Figure 4). Given these advantages, multiphase CT angiogram is applicable for both severe ischemic stroke and minor stroke.

CTA has become an important biomarker in the acute period to guide treatment with pharmacological and endovascular therapy, but it is also useful to predict natural history of both ischemic and hemorrhagic stroke. Predicting natural history or progression using CTA has been beneficial in the TIA/minor stroke population. Upto 10% of this population will develop symptom progression or recurrent stroke. In these patients, intracranial stenosis or occlusion on CTA has been shown to be an independent predictor; therefore, if neurovascular imaging is normal, patients can be discharged home with a high degree of confidence that they are at lower risk.

Although we focus on ischemic stroke in this article, CTA can also help to predict outcome in hemorrhagic stroke and a hemorrhagic...
angiography protocol should always be performed after an intracerebral bleed has been detected on NCCT. The detection of an occult arteriovenous malformation or aneurysm will guide immediate therapy. In spontaneous intracerebral hemorrhage (ICH), evidence of contrast extravasation (spot sign) on CTA refines the ability to predict hematoma expansion and mortality. The spot sign is thought to directly indicate active bleeding in acute ICH. Therefore, CTA can help guide treatment in acute ischemic and hemorrhagic stroke.

**Computed Tomographic Perfusion**

Computed tomographic perfusion is a technique that provides an estimate of cerebral blood flow. During computed tomographic perfusion, a rapid intravenous contrast bolus is administered and sections of the brain are repeatedly imaged. On the basis of the total amount and speed that blood flows through different vascular territories of the brain, this technique can assist in estimating potential areas of salvageable brain tissue/ischemic penumbra (Figure 5). However, the technique still requires standardization. Reproducibility and accuracy restricts the unique potential to provide clinically meaningful results. Varying studies have used different thresholds to define ischemic core and ischemic penumbra. Recent technological advancements have allowed a move toward fully automated software that allows processing and creation of perfusion maps robust to common artifacts. This can be performed in a relatively short period of time allowing rapid clinician interpretation in the acute period. However, the threshold values for ischemic core are likely to be dependent on how fast reperfusion can be achieved and hence, there may be no precise or uniform criteria possible.

**Magnetic Resonance Imaging**

MRI provides greater spatial resolution and physiological information compared with NCCT, at the expense of greater imaging time. Despite this expense, some centers rely on MRI to detect EIC because DW-MRI can detect ischemic changes within minutes of stroke onset. DWI allows clinicians to make an inclusive diagnosis of ischemic stroke, helping to differentiate true strokes from stroke mimics. The apparent diffusion coefficient map estimates the extent of cytotoxic edema and is a form of chemical imaging of water that represents ischemic brain tissue. Over time, the appearance of the diffusion and apparent diffusion coefficient abnormalities will reverse as the stroke moves into a subacute phase during the first 30 days, varying by ischemic tissue volume. The specific injury patterns that are identified on DWI help to date the time of onset, progression and resolution of strokes. Even after the acute treatment, MRI is helpful in determining stroke pathogenesis.
because it can help visualize small strokes and the distribution of stroke lesions that may not be visible on NCCT (Figure 6). This is especially true for minor ischemic strokes where the volume of ischemic tissue is low and posterior circulation strokes where the skull base impairs stroke visualization because of bony artifacts on NCCT.

**General Principles**

In general, the more advanced the imaging modality, the more time it takes. The diagnostic benefit gained from a more detailed image must be weighed against the time used to obtain it: an acute decision taken to defer treatment and obtain more information can be the same as a decision not to offer treatment. For each 15-minute delay in treatment, there is an estimated 4% reduction in the probability of good functional outcome. Each minute of onset-to-treatment time lost leads to the loss of an average of 1.8 days of extra healthy life. A key therapeutic principle is to gather adequate information to make a treatment decision and not delay treatment to obtain the perfect imaging information. This important aspect of the art of stroke treatment requires experience and a pragmatic approach. In summary, imaging in stroke syndrome presentations is the most important biomarker and fulfills multiple roles including understanding the cause of the stroke, estimating salvageable tissue and selecting appropriate patients for intravenous thrombolysis, endovascular treatment, and further treatment options.

**Acute Stroke Treatments: Outcome Assessment in Thrombolysis Trials**

Stroke is a disabling disease, with a large proportion of patients requiring ongoing care indefinitely. The process of recovering from a stroke is a dynamic process that is dependent on both the prevention of brain tissue death by acute medical interventions as well as the ongoing therapy. Thus, to measure the efficacy of stroke treatments, we must evaluate the immediate physical impairments as a measure of pathology, as well as the amount of recovery in a set time period. The majority of motor recovery occurs within 10 weeks, and on average...
The modified Rankin Scale (mRS), Barthel Index, and the National Institutes of Health Stroke Scale (NIHSS) have all been used to measure stroke outcomes.\(^4\4\) The original Rankin score is a categorical scale with the purpose of providing a reproducible categorization of functional neurological recovery after stroke.\(^4\5\) When it was used by the UK Transient Ischemic Study group in the 1980s, the scale was modified to its present form; the group further dichotomized their findings such that a score of 0 to 2 was considered nondisabling, and scores of 3 to 5 were disabling.\(^4\7\) Interim changes in the language were made to reflect the importance of determining handicap, particularly as it relates to the ability to live independently.\(^4\8\) The inclusion of an mRS score of 6 (death) was added primarily for the purpose of clinical trials.\(^4\6\)

The Barthel index is a summative 10-domain categorical scale that is scored to a maximum of 20 or scaled by a factor of 5 to a maximum of 100 point scale, grading ability to complete activities of daily living either independently or with help.\(^4\9\)\(^5\0\) Studies of the 2 scales found significant variability between measures of patients rated as independent as well as significant interobserver variability within the mRS.\(^5\1\)

The mRS is criticized for not assessing basic individual skills, including categories that are too broad and open to interpretation and not directly capturing cognitive impairment post stroke.\(^5\2\) Despite these criticisms, the mRS, scored at 90 days after stroke onset, has become the de facto international acute stroke treatment outcome measure. Indeed, some have suggested that the broadness, and interobserver variability may, in part, be responsible for some of the negative findings in early stroke trials that used simple dichotomized measures: independence (mRS, 0–2) versus dependent or death (mRS >2).\(^5\3\)\(^5\4\) The statistical simplicity of the binary outcome approach is advantageous in study design. A key drawback of this approach was observed in the European Cooperative Acute Stroke Study II (ECASS II) trial where choosing a primary outcome of mRS score of 0 to 1 yielded a neutral result, whereas the secondary outcome of mRS score of 0 to 2 was positive.\(^5\5\) Although dichotomizing the mRS end point results in loss of information, the scale is robust, broad enough that it identifies clinically meaningful outcome differences, and this has resulted in acceptance by regulatory agencies (Food and Drug Administration and European Medicines Agency) as the principal and standard outcome measure for acute stroke trials.\(^5\6\)

Other approaches to stroke outcome have been suggested. The global statistic, combining outcomes over different but related disability scales was reported by the National Institute of Neurological Disorders and Stroke (NINDS) trialists but has not had widespread adoption.\(^4\4\) Responder analysis, where outcomes are weighted according to baseline stroke severity, has typically still utilized the mRS because the primary measure with a responder being defined at varying levels of the mRS score assigned by some measure of baseline severity (eg, NIHSS score). Assessment of changes in disability across the whole spectrum of the mRS has been explored using proportional odds models (ordinal logistic regression) or using permutation tests.\(^5\7\) The shift analysis using ordinal logistic regression may provide greater power under specific distributions of the mRS scale.\(^5\8\)\(^5\9\) The positive endovascular trials reviewed below have all made use of ordinal logistic regression or the shift analysis.

### Intravenous Thrombolytic Drugs in Stroke Treatment: Urokinase, Streptokinase, and Tissue-Type Plasminogen Activator

Autopsies have long revealed thrombi in the carotid arteries of deceased stroke victims, and angiographic evidence of these thrombi was first shown in 1937 through an open technique. The finding that acute and sudden hemiplegia could be related to thrombosis of the carotid arteries resulted in initial surgical and medical efforts to open the occlusion.\(^5\7\) It was recognized early that the carotid artery occlusion may be associated with thrombosis in arteries further along the vascular tree, which may be the culprit lesion causing hemiplegia, and thus surgery to remove the carotid occlusion was not always beneficial.\(^5\8\) It was also recognized that action must be taken quickly because the neurological deficit may only be reversible for a short amount of time.\(^5\9\) Sussman and Fitch\(^6\0\) administered intravenously fibrinolysis (plasmin) to 3 patients with angiographically demonstrated occlusions of the middle cerebral artery (MCA) or anterior cerebral artery (ACA). The patient with MCA occlusion was treated within 6 hours and recovered, with follow-up angiography showing resolution of the filling defect. The trialists concluded that intravenously administered fibrinolysis may be beneficial in certain patients with angiographically proven occlusions.\(^5\8\) Unfortunately, expedient imaging of the vasculature was not routinely available for the use until ≈50 years later, and many of the early studies with intravenous fibrinolytic agents were hindered by the lack of any neuroimaging proof of occlusions or achieved recanalization. Anticoagulation with heparin, when stroke was diagnosed clinically without any neuroimaging proved to be dangerous with an increase in ICH.\(^6\1\)

In 1976, a pilot study with intravenous urokinase (initially discovered in 1947), dosed according to body weight, and using angiography to document intracranial occlusion for some, but not all of their patients, showed that intravenous urokinase was an effective thrombolytic agent but associated with an increase in ICH and no clinical improvement.\(^6\2\) Lower doses of urokinase were not associated with ICH, but equally without clinical improvement. One reason might be that urokinase is not selective for clot-bound plasminogen, and attention was directed toward alternate agents, such as streptokinase, which cleaves plasminogen to produce the active enzyme plasmin. In 1957, it was found that when peripheral thrombi were experimentally formed in human volunteers the administration of streptokinase induced intravascular thrombolysis.\(^6\3\) Streptokinase was evaluated for stroke in 40 patients who were treated within 72 hours of stroke onset with infusions given daily for 3 days. Most of the patients had angiographic evidence of thrombi resolution, but there was no significant improvement in the clinical outcome.\(^6\4\) When the same group evaluated whether streptokinase and heparin could be given in progressive strokes within 72 hours of onset, they found that there was significantly worse outcomes with increased...
risk of ICH. About 30 years later, streptokinase was used in multiple studies for myocardial infarction and was again looked at in the context of acute ischemic stroke; however, none of the trials, including the Multicenter Acute Stroke Trial-Europe (MAST-E), Multicenter Acute Stroke Trial-Italy (MAST-I), and the Australian Streptokinase study, were able to demonstrate a benefit for streptokinase administration versus placebo. MAST-E demonstrated increased parenchymal bleeding, without an increase in overall symptomatic hemorrhage. When the MAST-I was stopped early, analysis revealed that the use of streptokinase with aspirin significantly increased the risk of death in patients with stroke. Neither streptokinase nor urokinase is used for treatment of acute ischemic stroke.

Given the wide variability of recanalization with streptokinase, even more specific fibrinolytic agents with better recanalization rates were being actively investigated. The intravenous injection of rt-PA reduced the neurological damage induced by the injection of thrombi into the cerebral circulation of rabbits. An escalating dose of double chain rt-PA (duteplase) was examined in patients with proven occlusion on angiography and no hemorrhage on NCCT. Although the study was stopped early because of the withdrawal of the drug after a lawsuit, there was an increased recanalization of patients with occlusions of the M2 and M3 branches of the MCA. Associated with the use of duteplase in this study, the rates of parenchymal hematoma and hemorrhagic transformation were 10.6% and 20.2%, respectively. After this study, the safety of single-chain rt-PA (alteplase) was examined, and it was found that escalating doses were safe when administered within 90 minutes and within 91 to 180 minutes of symptom onset. It is alteplase that has been investigated and marketed throughout the world for the treatment of acute ischemic strokes.

The NINDS and tPA Stroke Study group recruited patients from January 1991 to October 1994 with the aim of comparing the use of 0.9 mg/kg IV alteplase to placebo in patients presenting with acute ischemic stroke, using a 24-hour NIHSS and a 3-month score on the Barthel Index, mRS, Glasgow coma scale, and NIHSS measure. The NINDS tPA Stroke trial showed that despite an increase in early intracranial hemorrhage, there was a 30% increase in good outcomes at 3 months in all the measured outcomes. The NINDS tPA Stroke trial resulted in licensure of alteplase for stroke treatment in a 3-hour window from symptom onset, and has had far reaching implications; the enrollment criteria used remain the framework for the published exclusion criteria for alteplase.

In the same year as the NINDS tPA Stroke Trial, ECASS found that alteplase at a dose of 1.1 mg/kg given within 6 hours of acute stroke onset did not result in improvement of the primary end points in the intention to treat analysis, but some of the secondary end points including Barthel index and mRS scores favored tPA treatment. There were a greater number of large intraparenchymal hemorrhages, attributed to a high rate of imaging protocol deviations, later treatment (≤6 hours) and use of the higher cardiac dose of alteplase. The trial was repeated as ECASS II with a decreased dose of alteplase to 0.9 mg/kg, tighter imaging controls, and examined for benefit in 2 strata: ≤3 hours from onset and from 3 to 6 hours from onset. It was neutral on the primary outcome (mRS, 0–1 at 90 days) but on post hoc analysis (not a predefined primary end point), the trial was positive on the mRS score of 0 to 2 outcome. Examination of treatment at later time windows (3–5 hours) in the Alteplase ThromboLysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS-B) trial was similarly neutral for benefit, and an increased number of hemorrhages were reported. The trials were analyzed together in 2004 using a pooled individual patient meta-analysis approach, including 2775 patients who had been treated within 360 minutes from stroke onset. The pooled data showed a clear benefit with earlier treatment after stroke onset that declined rapidly with time with the lower bound of the confidence interval (CI) approaching a neutral effect at 4.5 hours from stroke onset.

The ECASS III trial examined alteplase treatment in the 3- to 4.5-hour time window. Published in 2008 and with a median time of alteplase administration of 3:59 hours, ECASS III demonstrated an improvement in mRS at 90 days with intravenous alteplase. There was an associated increase in all ICH and symptomatic ICH. Although mortality remained unchanged, any delay in alteplase administration was associated with a greater risk of ICH. The Echoplanar Imaging Thrombolytic Evolution Trial (EPIThET) was a small neutral study, comparing placebo with alteplase from 3 to 6 hours after stroke onset, but with a focus on imaging. The purpose of the study was to assess for an imaging by treatment interaction. The primary clinical end point was the mRS at 90 days but shorter-term imaging outcomes were also assessed (eg, infarct growth and volume). Finally, in 2014, the largest of the intravenous thrombolysis trials using alteplase—the International Stroke Trial (IST)-3 was completed and published. IST-3 took almost a decade to complete and compared alteplase with placebo in patients with stroke in centers where intravenous alteplase was not the standard of care. Because the trial took over a decade to complete, it was susceptible to changes in stroke care and stroke treatment understanding over that period. Ultimately, it included many patients who were at the periphery of current treatment protocols (eg, >80 years of age and diabetics).

Although, individually these studies were neutral, a pooled analysis was updated in 2010 to reflect the inclusion of these trials, and demonstrated a clear treatment effect with evidence of sharp effect modification by time to treatment. The adjusted odds ratio (OR) of favorable outcomes was 2.55 when treated within 90 minutes of stroke onset (95% CI, 1.44–4.52), and gradually reduced to 270 minutes, beyond which there was no average benefit of alteplase after 270 minutes. The need for fast treatment times is further reflected in a time to treatment analysis from the Get-with-the-Guidelines US registry where analysis of 58,353 patients with thrombolysed stroke showed that with every 15 minutes of increment of faster onset to treatment time, there was reduced hospital mortality, reduced symptomatic ICH, increased achievement of independent ambulation, and chance of discharge to home. Recent trials have failed to show any average treatment benefit when alteplase was administered beyond the 4.5-hour time window, with no improvement in patient mortality at 6 months.
Meta-analysis of all the intravenous alteplase trials report that 29.3% of patients treated with placebo and a significantly greater number treated with intravenous alteplase (34.8%) achieved a favorable result defined as an excellent functional neurological outcome (mRS, 0–1). This is equivalent to 55 more patients alive and almost symptom free per 1000 patients.

All thrombolytic medications are associated with some risk of hemorrhage. In ischemic stroke, hemorrhage into the ischemic bed is the most severe complication and most often is fatal. Overall, the risk of ICH is low, particularly if treatment is initiated rapidly. Factors that are associated with increased hemorrhage risk include elevated serum glucose, evidence of EIC on brain imaging (ie, low ASPECTS score), or very low cerebral blood volume on computed tomographic perfusion. The current challenge is to determine whether we can predict who will benefit most from the intravenous alteplase and have the lowest risk for hemorrhage.

Newer studies have evaluated third-generation thrombolytic agents, including desmoteplase, reteplase, duteplase, and tenecteplase. Desmoteplase, isolated from the saliva of the Mexican vampire bat and synthesized in bioculture, was found to be effective in a 9-hour time window and was relatively safe at low doses. Subsequent trials of desmoteplase in late time windows are recently completed and did not show proven efficacy. Tenecteplase has superior fibrinolytic activity when compared with alteplase and has been found to be safe at smaller doses compared with the standard dose used in cardiology. In small studies, it has been shown to have increased reperfusion and improved functional outcomes. There is ongoing investigation into the widespread physiological effects of these drugs, as well as their potential use in acute stroke.

Tenecteplase is being used in the ongoing thrombolysis for minor ischemic stroke with proven acute symptomatic occlusion using tenecteplase (TEMPO-2) trial in an effort to find a safer and more effective treatment than alteplase.

### Intra-Arterial Thrombolytic Delivery

Since 1937, it has been possible to visualize intra-arterial occlusions using angiography. Early attempts to treat intracranial occlusion included surgery and intravenous administration of thrombolytic agents. It was not until the 1980s that the local intra-arterial delivery of thrombolytic agents was attempted. After initial case reports on intra-arterial administered thrombolytics, subsequent pilot studies reported treating patients within 8 hours from symptom-onset intra-arterial urokinase or streptokinase after occlusion was identified using angiography. Twenty patients were treated with a complete recanalization rate of 75% but 20% developed an ICH. Similar early results from treating vertebrobasilar occlusions with intra-arterial streptokinase or urokinase were reported. Despite these initial successes in recanalization, there was no ischemic stroke, hemorrhage into the ischemic bed is the most severe complication and most often is fatal. Overall, the risk of ICH is low, particularly if treatment is initiated rapidly. Factors that are associated with increased hemorrhage risk include elevated serum glucose, evidence of EIC on brain imaging (ie, low ASPECTS score), or very low cerebral blood volume on computed tomographic perfusion.

The current challenge is to determine whether we can predict who will benefit most from the intravenous alteplase and have the lowest risk for hemorrhage.

### Intra-Arterial Thrombolytic Delivery

Since 1937, it has been possible to visualize intra-arterial occlusions using angiography. Early attempts to treat intracranial occlusion included surgery and intravenous administration of thrombolytic agents. It was not until the 1980s that the local intra-arterial delivery of thrombolytic agents was attempted. After initial case reports on intra-arterial administered thrombolytics, subsequent pilot studies reported treating patients within 8 hours from symptom-onset intra-arterial urokinase or streptokinase after occlusion was identified using angiography. Twenty patients were treated with a complete recanalization rate of 75% but 20% developed an ICH. Similar early results from treating vertebrobasilar occlusions with intra-arterial streptokinase or urokinase were reported. Despite these initial successes in recanalization, there was no clear difference in recanalization rates with urokinase versus alteplase and it remained uncertain if there was a thrombolytic agent of choice. However, outcome was related instead to where the occlusion was found; occlusions at the carotid siphon and M1 branch or pure MCA branch occlusion had a better outcome than when the MCA and anterior cerebral artery branches were occluded simultaneously or when the MCA trifurcation was occluded.

In 1998, before the widespread use of CTA, the ProLyse in Acute Cerebral Thromboembolism (PROACT) study demonstrated the safety of using cerebral angiography to identify patients with occlusion and to deliver prourokinase to the affected M1 and M2 branches of the MCA. In PROACT II, 40% of the patients who received therapy had an independent outcome (mRS, 0–2) compared with 25% in the control group, and this improvement was associated with significantly greater recanalization rates. To enrol 180 subjects, 474 patients underwent diagnostic/screening angiograms, implying that a high proportion of patients with major stroke syndromes at presentation do not have major intracranial arterial occlusion in the anterior circulation.

The Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT), with a similar design using intra-arterial urokinase study done in Japan, included only those patients with M1 or M2 occlusions demonstrated on diagnostic angiogram. The study ended early, when intravenous alteplase was approved in Japan in 2005; however, among the enrolled patients there were significantly more patients who had a complete neurological recovery (NIHSS ≤1) at 90 days, but no difference in 90-day mRS.

The Emergency Management of Stroke bridging trial combined both intravenous and intra-arterial alteplase within 3 hours of stroke onset and successfully enrolled just 35 patients. There was no difference in dichotomized mRS, despite increased recanalization rates in the intervention group. The first Interventional Management of Stroke (IMS) trial, a prospective cohort study enrolled patients treated with intravenous alteplase at reduced dose (0.6 mg/kg) to a maximum dose of 60 mg and then proceeded immediately to additional intra-arterial delivery of additional alteplase. The mean times from symptom onset to intravenous alteplase treatment and intra-arterial alteplase treatment was 136±30.2 minutes and 217±46.7 minutes, respectively. Despite the mean 81-minute delay to intra-arterial therapy, there was a statistically significant improved 3-month functional outcomes, without an increase in symptomatic ICH (there was an increased in asymptomatic hemorrhage). Reflecting the technological developments in treatment, the study was repeated as the IMS II trial, to include microcatheter with ultrasound technology. Again, improvement of functional scores at 3 months was noted, with similar safety profiles to the NINDS trial but neither trial had a concurrent control group and not enough patients were treated with the EKOS MicroLys Ultrasound catheter to provide convincing evidence of superiority of the approach. The Randomized Controlled Trial on Intra-Arteral Versus intravenous Thrombolysis in Acute Ischemic Stroke (SYNTHESIS) trial, an Italian pilot study, aimed to treat with intravenous alteplase within 3 hours and intra-arterial alteplase within 6 hours. Again safety and efficacy were demonstrated with no significant differences in adverse events.

With the technological advances in imaging, the REcanalization using Combined intravenous Rt-PA and NeurointerventionALgOrithm for acute Ischemic Stroke (RECANALISE) study, a cohort study, required CTA or magnetic resonance angiography to identify intracranial
occlusions. Recanalization rates at 24 hours were 52% in the intravenous group, when compared with 87% in the intra-arterial alteplase group, independent of the site of occlusion. However, there was no significant difference in those patients who achieved a favorable mRS at 90 days.110

**Acute Stroke Treatments:**

**Endovascular Treatments**

With the invention of thrombectomy devices, a new method for the treatment of strokes was initiated. Early trials were neutral or negative. Synthesis Expansion: A Randomized Controlled Trial on Intra-Arterial Versus intravenous Thrombolysis in Acute Ischemic Stroke (SYNTHESIS EXPANSION) randomized patients in a 1:1 ratio to medical care with intravenous alteplase or directly to endovascular treatment. A NCCT head was required to rule out hemorrhage and angiography was used to direct therapy, with intra-arterial alteplase being given using the intravenous alteplase dosing scheme (0.9 mg/kg to a maximum dose of 90 mg).111 If no occlusion was seen, alteplase was injected into the presumed affected artery. The use of an endovascular thrombectomy device was at the discretion of the treating team, and of the 109 patients who received intra-arterial alteplase, 56 patients had an additional device used. The adjusted OR of achieving a favorable mRS at 3 months was not significantly greater for endovascular compared with medical treatment (OR, 0.71; 95% CI, 0.44–1.14; P=0.16). There was a significant difference in the time to treatment between the intravenous alteplase group compared with endovascular treatment; endovascular treatment was an hour slower.111

Although occlusions were not visualized as a criterion for enrollment, in Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) Trial, MRI measures of infarction and perfusion were assessed before treatment.112 Randomization was stratified by MR diffusion–perfusion signature. Patients were then randomized in a 1:1 ratio to endovascular treatment with the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) retriever or best medical therapy. It was hypothesized that the patients who would most likely benefit from endovascular thrombectomy could be identified based on a substantial ischemic penumbra and small predicted core.113 Patients were treated within an 8-hour time window, and unfortunately there was a low rate of recanalization, which most probably reflected the use of older thrombectomy devices. There was no significant improvement in favorable mRS scores, even if patients were divided into those with favorable MR diffusion–perfusion defined penumbral patterns.

IMS III was the largest of these 3 trials, randomizing subjects in a 2:1 ratio to endovascular therapy or control over and above a baseline of all patients receiving intravenous alteplase. The time to endovascular therapy was shown to be 32 minutes longer than to intravenous therapy.114 Importantly, CTA was only used later in the trial because its use became more prevalent in routine care. The development of stent retrievers also occurred during the trial, with the Solitaire stent retriever being used in later stages for only a handful of patients. The lack of clear imaging evidence of occlusions and the use of older thrombectomy devices during the trial likely contributed to the neutral overall result.114 Further analysis of the IMS III trial indicated that CTA was not associated with increased time to intravenous alteplase administration, but was associated with decreased time to reperfusion during endovascular treatment perhaps because the affected neurovascular area had already been definitely identified or because the sites that were using CTA had better established workflow for treatment.115 Subgroup analysis of those patients with definite occlusions on CTA indicated that there was a trend toward improved functional outcomes with endovascular treatment with good safety data.116

The changes incorporated in imaging technology in IMS III are also mirrored by advancements in thrombectomy devices. The first thrombectomy device is the MERCI retriever, which is described as flexible and corkscrew shaped.117 This device was followed by several iterations in design and finally led to the current stent retrievers, including Solitaire and Trevo, which are more flexible. As reviewed elsewhere, it has been shown that the Solitaire and the Trevo devices are superior to the MERCI device.117 Therefore, the earlier studies that primarily relied on MERCI devices were disadvantaged by technology.

The first reported positive endovascular trial was the Multicenter Randomized Clinical Trial of Endo-vascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN), with results being announced in late 2014. In this study, 500 patients from across the Netherlands who had proven occlusion of the distal internal carotid artery, or the proximal segments of either MCA or anterior cerebral artery with an NIHSS of ≥2 were enrolled and randomized in a 1:1 ratio to endovascular treatment or best medical therapy.106 Initiation of the endovascular treatment occurred within 6 hours of stroke onset, and intravenous alteplase could be given according to European guidelines. Retrievable stents were used in the majority of patients. The mRS shift analysis (ordinal logistic regression) showed a significant improvement in outcomes favoring the endovascular group (adjusted OR, 1.67 with a 95% CI, 1.21–2.30) at 90 days.106

The Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial was halted in November 2014 and published in March 2015, and again used a shift analysis to explore whether rapid endovascular treatment would result in overall lower mRS, when compared with best medical therapy, including intravenous alteplase where appropriate.17 Patients with disabling stroke were enrolled within 12 hours of onset, and only included if imaging revealed all of the following: small infarct core defined as ASPECTS score <6, an occlusion of the anterior circulation involving a proximal artery and moderate to good collaterals. The trialists emphasized the importance of speed in achieving recanalization, and the aim was to achieve reperfusion within 90 minutes from the initial NCCT scan slice. The trial was stopped early after interim analysis demonstrated overwhelming efficacy of the treatment, with the primary analysis revealing an OR toward improvement across all mRS score of 2.6 (95% CI, 1.7–3.8; P<0.001). The traditional, dichotomized analysis comparing subjects who attained a mRS score of 0 to 2 compared with 3 to 6 showed 53.0% of patients attaining a good outcome in the...
intervention group and 29.3% in the control group (rate ratio, 1.8; 95% CI, 1.4–2.4; \(P<0.001\)). Mortality was significantly reduced although the rates of ICH were not significantly different. The success of this study reflects the use of careful imaging selection, the use of retrievable stents in most (86.1%) of the subjects, with concurrent use of alteplase in 72.7%, and a rapid rate of reperfusion (with a median time from NCCT and CTA to reperfusion of 84 minutes).

The Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial (EXTEND-IA) trial was a phase 2 study differing from the previous 2 trials in that the primary outcome was a surrogate composite based on imaging evidence of reperfusion and clinical measures.\(^{18}\) Inclusion required stroke onset within 6 hours of starting endovascular procedure, and the Solitaire stent retriever was used in all sites. All patients were selected using multimodal computed tomographic perfusion to define a salvageable penumbra. Seventy patients were enrolled before the trial was stopped after the positive results of MR CLEAN were announced. The results showed an increase in reperfusion, and an improved clinical outcome on the mRS at 90 days with 71% of patients achieving independence after endovascular treatment, compared with 40% after intravenous tPA (\(P=0.01\)).

The Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset (REVASCAT) study, carried out in north-east Spain, was halted early after equipoise was lost with the release of the MR CLEAN data.\(^{20}\) In this study, 206 patients with proximal occlusions of anterior circulation defined by CTA were randomized to endovascular treatment or best medical care, if they presented within 8 hours of stroke onset. The OR of improving 1 point or more on the mRS was significantly greater in the endovascular group at 1.7 (95% CI, 1.05–2.8) with no increase in ICH. In addition showing a significantly greater shift to improved outcomes, this study also showed an improvement with infarct volume being smaller (median values, 16.3 mL versus 38.6 mL) with endovascular therapy (\(P=0.02\)). Importantly, this study excluded those patients who responded early to intravenous therapy, such that the occlusion had to be redemonstrated after intravenous therapy was given before thrombectomy.

The Solitaire with the Intention for Thrombectomy (SWIFT PRIME) trial was published in June 2015 together with the REVASCAT study.\(^{19}\) Patients with confirmed anterior circulation occlusions were randomized if they presented within 6 hours of stroke onset to receive thrombectomy with stent retrievers or best medical therapy. Both the shift in disability on the mRS and the proportion of independent patients were significantly improved with thrombectomy (\(P<0.001\)). There were no significant changes in serious adverse events.

There are now 5 positive trials favoring the use of thrombectomy in proximal occlusions affecting the anterior circulation.\(^{19}\) We await the publication of 3 other completed trials, Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke (THRACE), Assess the Penumbra System in the Treatment of Acute Stroke (THERAPY), and the Pragmatic Ischemic Stroke Thrombectomy Evaluation (PISTE) trials, which have been presented in abstract form.\(^{119}\) The development of imaging techniques, which allow the identification of occlusions, as well as the affected vascular bed have allowed thrombectomy to proceed at an unprecedented fast pace. The speed of reperfusion has also been aided by the recognition of the importance of workflow patterns.\(^{120}\) The development of new stent retrievers has also been a significant technical advance. Finally, sophisticated statistical analysis has allowed a more uniform and sensitive approach to measuring outcomes in trials.\(^{53}\) The common theme to all of these trial results is that it is the combination of these developments that have led to a new standard of care. None alone would have resulted in a better outcome. Now, it will be important to focus on systems issues that will allow us to offer these interventions universally, even if strokes occur away from cities with stroke centers and endovascular catheter laboratories.

The evolution of endovascular therapy has produced a consistent true ischemia–reperfusion model in human ischemic stroke. It is this model, ischemia–reperfusion, which has been studied so extensively in preclinical models in the past. Most adjuvant or so-called neuroprotective agents have been shown to reduce infarct volume and improve neurobehavioral outcome in rodent models of ischemia–reperfusion. Tellingly, in rodent models of permanent ischemia, these same agents have shown limited efficacy. The failure of thousands of molecules touted for stroke therapy during the past 25 years has left a black cloud over ongoing development of adjuvant and neuroprotective agents. However, now is the exact time to be testing these molecules. Strategies focussing on excitotoxicity (NMDA [N-methyl-D-aspartate] receptor blockade), reperfusion injury,\(^{121,122}\) and the health of the neurovascular unit may yet prove to be useful in the human ischemia–reperfusion model. Retesting of old molecules may be newly justified, particularly those that were not marred by toxicity.\(^{123–125}\) Newer molecules, such as NA-1, will be evaluated in this paradigm.\(^{126}\) Hypothermia, a proven multimodal, effective physical approach to cytoprotection needs to be retested in this model.\(^{127}\) Although there are no currently accepted adjuvant pharmacological treatments for acute stroke currently, this is a future blank-slate area for clinical research.

**Hyperacute Prevention of Acute Cerebral Ischemia**

Patients with minor stroke or TIA or early dramatic clinical recovery after reperfusion of major ischemic stroke are at the highest risk of early deterioration. The commonest clinical scenario occurs with minor stroke or TIA. These patients will not generally be appropriate for thrombolytic therapy but it is equally important to treat them hyperacutely to prevent progression to major stroke. The highest risk of stroke progression or recurrence is in the first hours to days from initial symptom onset, with almost 7% risk at 48 hours and a 10% risk by 7 days, even for patients with initial mild clinical presentations.\(^{128,129}\) Most recurrent or progressive events occur overnight after the initial ictus, with a median time of 1 day.\(^{31}\) CTA
can help risk stratify to determine which patients are at highest risk of recurrence. A basic assessment of stroke mechanism is vital to the choice of hyperacute preventive therapy. The many proven treatments to prevent early stroke recurrence are summarized below.

**Acute Blood Pressure and Antiplatelet Treatments**

Any potential benefits of rapid blood pressure lowering in acute ischemic stroke must be balanced against the potential risks of worsening cerebral ischemia from altered autoregulation/perfusion. In the absence of definitive randomized evidence, guidelines for the early management of high blood pressure in patients with acute ischemic stroke are weak and based on the consensus opinion only. Physiologically, blood pressure may be guided by vessel status (if known), avoiding blood pressure lowering acutely while the vessel is occluded and then considering blood pressure lowering when the vessel is known to be open. Until further evidence is available, blood pressure–lowering therapy should be used carefully and on an individual basis during the acute phase.130

Low-dose aspirin (75–150 mg daily) is an effective antiplatelet regimen for long-term use for patients at increased risk of occlusive vascular events and is the current standard of care for secondary prevention after an acute ischemic stroke or TIA.131 It is cheap, safe, and effective but has a relatively small effect size. The potential use of combining platelet antiaggregants with different mechanisms of action proved successful with aspirin plus extended-release dipyridamole.132 Subsequent trials have explored the effects of combined antiplatelet therapies as a possible superior alternative management. In 2007, the Fast Assessment of Stroke and Transient ischemic attack to prevent Early Recurrence (FASTER) trial reported that early aggressive dual antiplatelet therapy (aspirin plus clopidogrel) for 90 days may be associated with a reduction in recurrent ischemic cerebrovascular events, although there was a slight increased rate of hemorrhagic complications. The absolute reduction of 3.8%, 3.3%, and 7.0% during 90 days for the primary (all stroke), secondary (all stroke, myocardial infarction, and vascular death), and tertiary outcomes (all stroke, TIA, acute coronary syndrome, and all-cause death), respectively, was found for the combination of aspirin and clopidogrel over aspirin use alone but was statistically not significant because the trial was underpowered as a pilot study.133 Further studies of aspirin plus clopidogrel showed no significant reduction in vascular events, but demonstrated increased risk of moderate-to-severe bleeding over clopidogrel in the Management of Atherothrombosis with Clopidogrel in High-risk patients with recent transient ischemic attack or ischemic stroke (MATCH) trial and in The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial.134 Finally, in 2013, the benefit of treatment initiation within 24 hours after cerebral ischemia with combination of clopidogrel and aspirin was proven in the Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial, a study which repeated the FASTER protocol design in a Chinese population.135 The combination therapy for 21 days was superior to aspirin alone for reducing the risk of stroke in the first 90 days (hazard ratio, 0.63; \( P<0.001 \)) and did not increase the risk of hemorrhage. CHANCE was a multicenter, randomized, double-blind, placebo-controlled trial carried out exclusively in China. Because of differences in stroke pathogenesis and in particular the much higher prevalence of intracranial atherosclerotic disease in China, it has been postulated that the results might not be generalizable to other populations. Although immediate initiation of dual antiplatelet is supported by the CHANCE trial, the lingering questions of the optimal duration of therapy and applicability to other populations remains. The Platelet-Oriented Inhibition in New TIA and minor ischemic stroke (POINT) trial is currently enrolling North American patients with inclusion/exclusion criteria similar to the CHANCE trial and compares clopidogrel versus therapy over and above open-label aspirin (dose at the discretion of the investigator).136 To evaluate a potent antiplatelet agent as a superior alternative of the present standard of care, the Acute Stroke Or Transient Ischemic Attack (TREAT) With Aspirin or Ticagrelor and Patient OutcomeES (SOCRATES) trial has completed enrollment of patients’ worldwide comparing secondary prevention with ticagrelor (P2Y12 receptor inhibitor) versus aspirin.137 The Triple Antiplatelets for Reducing Dependency After Ischemic Stroke (TARDIS) trial is enrolling patients and comparing the safety and efficacy of intensive (combined aspirin, clopidogrel, and dipyridamole) versus guideline antiplatelet therapy, both given for 1 month.138 Results of these trials will hopefully provide future guidelines on optimal antiplatelet treatment in the acute and subacute phase of ischemic strokes and TIA.

All patients within 24 hours of an acute cerebrovascular ischemic event should be considered for immediate antiplatelet therapy (if thrombolysis is not administered) or enrollment in a clinical trial testing early antithrombotic therapy. If intravenous, intra-arterial thrombolysis, or endovascular treatment have been performed, the patient should be closely monitored and a follow-up imaging performed to exclude large hemorrhagic transformation or parenchymal hematoma before initiating antiplatelet therapy.

**Intracranial Oclusive Disease**

Large artery intracranial oclusive disease because of intrinsic atherosclerotic disease has emerged as a major stroke mechanism worldwide, especially in Asian patients, and has a high risk of stroke recurrence both early and late of ≤20% within 2 years.139 Preventive treatment with warfarin over aspirin showed an excess of hemorrhages with warfarin treatment but no significant efficacy.140 Early aggressive medical management (dual antiplatelet therapy, intensive cholesterol–lowering management, and a lifestyle-modification program) for 3 months is beneficial over stenting during short- and long-term follow-up period. The rates of any stroke (\( P=0.0468 \)) and any major hemorrhage (\( P=0.0009 \)) were significantly lower in the aggressive medical management group of the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial compared percutaneous transluminal angioplasty.141 SAMMPRIS did not compare aggressive medical management to single-antiplatelet therapy. This stroke subtype is more common in Asian...
patients, and the CHANCE and FASTER trials have already established the safety of early dual antiplatelet therapy in this patient population. However, subgroup analysis of CHANCE showed that for patients with intracranial artery stenosis clopidogrel plus aspirin is not significantly different than aspirin alone in preventing recurrent stroke.\textsuperscript{142}

**Atrial Fibrillation**

Atrial fibrillation is a treatable major risk factor for ischemic stroke. Direct oral anticoagulants have a lower risk of intracranial hemorrhage and will likely replace vitamin K antagonists because of efficacy and ease of use. Direct oral anticoagulants are either direct thrombin inhibitors (dabigatran) or factor-X inhibitors (apixaban, rivaroxaban, and edoxaban). Recent data from the Risk of early stroke recurrence in patients with Atrial Fibrillation (RAF) study showed that the best time for initiating anticoagulation treatment for secondary stroke prevention is 4 to 14 days from stroke onset: hazard ratio was 0.53 (95% CI, 0.30–0.93) for primary study outcome (composite of stroke, TIA, symptomatic systemic embolism, symptomatic cerebral bleeding, and major extracranial bleeding within 90 days).\textsuperscript{143} Twelve percent of patients in this study were treated with novel oral anticoagulants and had low risks for both symptomatic intracranial bleeding (2.1%) and ischemic events (4.3%) during follow-up. Because dabigatran may be associated with lower intracranial hemorrhage rates than the other novel anticoagulants, the Dabigatran Following Transient Ischemic Attack and Minor Stroke (DATAS II) study (ClinicalTrials.gov Identifier: NCT02295826) will assess the safety of early anticoagulation versus aspirin in mild-to-moderate ischemic stroke and TIA of yet unknown but possibly cardioembolic mechanism. Future randomized trials assessing the efficacy of the other novel oral anticoagulants in the acute phase of stroke in patients with atrial fibrillation are warranted.

**Large Vessel Disease**

Carotid artery stenosis causes ≤10% of all ischemic strokes. Carotid revascularization can be achieved by carotid endarterectomy, which has been performed for the past 60 years, or carotid artery stenting (CAS), which has emerged as a treatment alternative in recent years. A recent meta-analysis favored carotid endarterectomy over CAS for the prevention of 30-day post procedural stroke recurrence and mortality.\textsuperscript{144} During the periprocedural period, there was higher risk of stroke with CAS and a higher risk of myocardial infarction with carotid endarterectomy within the North American Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST).\textsuperscript{145} Complications arise from the wire passing through the atherosclerotic lesion and stent placement might cause many small emboli. Another theoretical drawback of CAS is the possibility of in-stent restenosis because of neo-intimal hyperplasia and hemodynamic turbulence; however, this seems to be more theoretical than real based on long-term follow-up of the International Carotid Stenting Study (ICSS) and CREST studies.\textsuperscript{146} Nevertheless, if a patient has a severe risk for complications under general anesthesia or the lesion is surgically not accessible, CAS is a valuable alternative in individual patients. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) trial reported
carotid endarterectomy to be highly beneficial in patients with high-grade stenosis (>70%) and recent TIA or nondisabling strokes.\textsuperscript{147} Pooled analysis of NASCET and European Carotid Surgery Trial (ECST) data confirmed that urgent revascularization within the first 14 days after minor/moderate ischemic strokes with NIHSS <10 and TIA patients with >50% internal carotid artery stenosis is still safe and beneficial.\textsuperscript{148} Although carotid revascularization in symptomatic patients is not an emergency treatment, it is an urgent treatment that should be undertaken within days of the ictus.\textsuperscript{149}

**Small Vessel Disease**

Lacunar stroke is the most problematic in the modern era because the vascular pathology cannot be imaged acutely. Lacunar stroke is suspected based on the presentation and history. A short course of dual antiplatelet therapy in minor strokes or TIA was beneficial with a lower 3-month stroke recurrence rate among Chinese patients in the CHANCE trial.\textsuperscript{150} However, there is no evidence to support the use of long-term dual antiplatelets in this scenario. The Secondary Prevention of Small Subcortical Strokes Trial (SPS3) trial showed similar rates for recurrent stroke using dual antiplatelets versus aspirin alone (2.5% versus 2.7%) but an increased risk of bleeding and higher mortality in the dual antiplatelet group.\textsuperscript{151}

**Stroke Causes in Younger Patients**

Twenty-five percent of young patients with stroke present with extracranial artery dissection. Mass effect from the intramural hematoma causes vessel occlusion and hypoperfusion or more commonly stroke is caused by arteroembolism from a thrombus at the site of the arterial intimal tear; transcranial Doppler studies have shown a high rate of microembolic signals, a marker of embolization.\textsuperscript{152} The Cervical Artery Dissection in Stroke (CADISS) trial evaluated antiplatelet therapy (single and dual) compared with antiocoagulation within 7 days of onset in patients with cervical artery dissection.\textsuperscript{153} The trial had such a low recurrence rate (overall 2% of ipsilateral 3 months) that it was underpowered to show a significant difference between the 2 treatment arms. Further studies are needed to determine whether there is a definite benefit of antiocoagulation during antiplatelet therapy in the acute setting in patients with extracranial cervical artery dissection. Currently, the use of anticoagulants (eg, intravenous unfractionated heparin) versus antiplatelets seems to be largely determined by opinion and geographic custom. We favor dual antiplatelets (aspirin and clopidogrel) in most patients with stroke because of extracranial cervical artery dissection and reserve anticoagulants for situations where there is imaging evidence of intravascular nonocclusive thrombus.

**Uncommon Stroke Pathogeneses**

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome is one of the most frequent maternally inherited mitochondrial disorders and a possible pathogenesis of stroke in younger patients. One of the single-gene disorders causing subcortical or lacunar strokes in young patients is cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). There are no disease-specific interventions for acute treatment in either of these conditions.
Pregnancy-associated stroke is rare but causes serious morbidity and long-term disability in young women and typically occurs in the third trimester and in the first 6 weeks of postpartum. There is an increased risk of stroke because of physiological changes in circulatory dynamics, coagulation changes, connective tissue integrity, and immune responses during pregnancy. Stroke may occur with common mechanisms (eg, arterial dissection and cardioembolic stroke), lower limb deep venous thrombosis associated with paradoxical embolus, cerebral venous sinus thrombosis, posterior reversible encephalopathy syndrome, hemolytic anemia, elevated liver enzymes, and low platelet syndrome with intracranial hemorrhage syndrome, or reversible cerebral vasospasm syndrome. In addition to possible antplatelet therapy, these pathologies will each need additional individual treatment that would exceed the scope of this article.

**Supportive Treatment**

The hemodynamic status of the patient can influence the severity of his stroke symptoms. Fluid resuscitation, positioning of the patient (head down), and, in rare cases, vasopressors might help to sustain appropriate cerebral perfusion pressure.

**Summary**

The protean manifestations of intra- and extracranial thrombi reflect the diverse pathogeneses and anatomic localizations of stroke syndromes. Although we have known that large and small vessel occlusions are responsible for sudden neurologic changes for >80 years, it is only recently that we have been able to image occlusions with adequate resolution and within a reasonable time frame to optimize treatment. Imaging has now become the essential biomarker for stroke and continues to influence our hyperacute treatment decisions. Intravenous fibrinolytic drugs have been safely administered for years, whereas more recent advances in imaging technology and thrombectomy devices, as well as more sophisticated statistical analysis and the optimization of work flow in the emergency room environment have collectively resulted in endovascular treatment as the new standard of care for proximal occlusion in the anterior cerebral circulation. All patients, regardless of eligibility for either of these acute treatments, will benefit from hyperacute secondary prevention that is tailored to their stroke pathogenesis. Both hyperacute treatment and hyperacute secondary prevention can help reduce death and disability in stroke syndromes.

The principles of stroke treatment now rely on rapid transportation of patients to a stroke center, early use of multimodal imaging, and rapid implementation of treatments. The whole spectrum of stroke ranging from minor to major symptoms has the potential to be catastrophic and should lead to immediate treatment initiation. Neurovascular imaging and speed of diagnosis and treatment are themes of stroke therapy.

**Disclosures**

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