Cerebrovascular Disease

Article 1: Epidemiology and Primary Prevention of Stroke


ABSTRACT

PURPOSE OF REVIEW:
This article provides an update on the epidemiology and prevention of a first stroke. Risk factor modification plays a large role in stroke prevention. Strategies for early intervention, particularly for hypertension, are critical for reducing stroke morbidity and mortality.

RECENT FINDINGS:
Because of the new criteria for hypertension, more people are now classified as hypertensive and can benefit from lifestyle or medical management. Direct oral anticoagulants have made it easier to safely treat patients with atrial fibrillation and are now considered first-line therapy for patients with an additional stroke risk factor.

SUMMARY:
Primary prevention of stroke is essential for maintaining brain health throughout the life span. Adherence to a healthy lifestyle and routine screening for stroke risk factors can promote healthy, stroke-free aging.

KEY POINTS

- Stroke is the fifth leading cause of death in the United States.
- Of those who survive stroke, half have moderate to severe disability.
- Blood pressure should be managed to achieve a goal of <130/80 mm Hg.
- Diabetes mellitus is an independent risk factor for stroke.
- The CHA2DS2VASC (congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, stroke, vascular disease, age 65 to 74 years, sex category [female sex]) score is useful for selecting patients with atrial fibrillation who would benefit from anticoagulation.
- The role of cholesterol and its subfractions in first stroke (ie, primary stroke prevention) is complicated, and studies have been inconsistent.
- Neurologists should counsel patients on the importance of smoking cessation and offer therapies proven to achieve abstinence.
- Several trials have demonstrated the protective effect of physical activity in reducing stroke risk.
The risk of stroke is 5 to 30 times higher in patients with chronic kidney disease, especially in patients on dialysis. Blood pressure control is particularly important to prevent stroke in this population.

The risk of stroke is higher with abstinence versus low intake of alcohol.

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**Article 2: Update on Treatment of Acute Ischemic Stroke**


**ABSTRACT**

**PURPOSE OF REVIEW:** This article provides an update on the state of the art of the treatment of acute ischemic stroke with particular emphasis on the indications for reperfusion therapy.

**RECENT FINDINGS:** In addition to the previously established indications for intravenous (IV) thrombolysis with recombinant tissue plasminogen activator (rtPA) within 4.5 hours of stroke symptom onset and endovascular therapy with mechanical thrombectomy for patients with large artery occlusion who can be treated within 6 hours of symptom onset, recent randomized controlled trials have now established new indications for emergency reperfusion in patients with wake-up stroke or delayed presentation (up to 24 hours from last known well in the case of mechanical thrombectomy). Identification of patients who may benefit from acute reperfusion therapy within this extended time window requires screening with perfusion brain imaging or, in the case of IV thrombolysis for wake-up strokes, emergency brain MRI. Collateral status and time to reperfusion remain the primary determinants of outcome.

**SUMMARY:** Timely successful reperfusion is the most effective treatment for patients with acute ischemic stroke. Recent evidence supports the expansion of the time window for reperfusion treatment in carefully selected patients.

**KEY POINTS**

- Prompt reperfusion is the most effective treatment for patients with acute ischemic stroke.
- The three principles of acute stroke therapy are to achieve recanalization of the occluded vessel (and reperfusion of the ischemic tissue), to optimize collateral flow, and to avoid secondary brain injury.
- The ischemic penumbra is the region of hypoperfused brain that can still be viable with prompt recanalization of the occluded artery.
- Collateral flow is responsible for the temporary preservation of the ischemic penumbra.
- No neuroprotective agent has been proven to be beneficial for acute ischemic stroke in clinical trials.
- IV thrombolysis with recombinant tissue plasminogen activator (rtPA) and endovascular thrombectomy with a retrievable stent are both solidly established treatments for appropriate candidates with acute ischemic stroke.
- Time to reperfusion is a major determinant of outcome in acute ischemic stroke.
- Randomized placebo-controlled trials have demonstrated that IV thrombolysis with rtPA is beneficial for patients with acute ischemic stroke up to 4.5 hours from symptom onset.
- Most cases of symptomatic intracerebral hemorrhage are caused by reperfusion injury causing hemorrhagic transformation of an already severe stroke.

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Endovascular therapy with mechanical thrombectomy substantially improves functional outcomes in patients with acute stroke from a proximal intracranial artery occlusion (internal carotid artery or M1 segment) especially when the intervention is performed within 6 hours of symptom onset.

Some previously cited contraindications for IV thrombolysis have been revisited, thus expanding the pool of patients who can be considered good candidates for this treatment.

Benefit from IV thrombolysis is much greater in the first 90 minutes from symptom onset.

Candidates for endovascular stroke therapy are patients with severe neurologic symptoms, no major ischemic changes on the baseline CT scan, good prestroke functional status, and early presentation.

Mechanical thrombectomy can be attempted when IV thrombolysis does not result in rapid clinical improvement and also in patients who are ineligible for IV rtPA.

Careful assessment of brain imaging is necessary to exclude a large established infarction (core).

The optimal radiologic method to select candidates for endovascular therapy is not yet established, but assessment of early ischemic changes on CT, evaluation of collaterals on CT angiography, and CT perfusion or MRI diffusion/perfusion are all available options.

Patients with wake-up strokes and those with stroke of unknown time of onset presenting within 24 hours of the last time when they were known to be well should be treated with endovascular thrombectomy if they have a large intracranial artery occlusion and evidence of salvageable tissue on perfusion imaging.

It is prudent not to administer IV thrombolysis in patients taking the novel oral anticoagulants (dabigatran, rivaroxaban, apixaban, edoxaban) because readily available tests in the emergency department cannot quantify the degree of active anticoagulation.

Patients with mild or rapidly improving strokes who present within the time window for IV thrombolysis and still have disabling symptoms at the time of the evaluation should probably be offered treatment with rtPA.

Patients with minor, nondisabling stroke symptoms should not be currently considered candidates for IV thrombolysis.

Although patients with basilar artery occlusion were not included in the randomized controlled trials of IV thrombolysis or mechanical thrombectomy, these patients should be treated with acute reperfusion therapies because of their dismal prognosis if recanalization cannot be achieved.

Mobile stroke units have been shown to provide a safe way to start thrombolysis in the prehospital setting.

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**Article 3: Neuroimaging in Acute Stroke**


**ABSTRACT**

PURPOSE OF REVIEW:

This article describes how imaging can be used by physicians in diagnosing, determining prognosis, and making appropriate treatment decisions in a timely manner in patients with acute stroke.

RECENT FINDINGS:

Advances in acute stroke treatment, including the use of endovascular thrombectomy in patients with large vessel occlusion and, more recently, of IV thrombolysis in an extended time window, have resulted in a paradigm shift in how imaging is used in patients with acute stroke. This paradigm shift, combined with the understanding that “time is brain,” means that imaging must be fast, reliable, and available around the clock for physicians to make appropriate clinical decisions. CT has therefore become the primary imaging modality of choice. Recognition of a large vessel occlusion using CT angiography has become essential in identifying patients for...
endovascular thrombectomy, and techniques such as imaging collaterals on CT angiography or measuring blood flow to predict tissue fate using CT perfusion have become useful tools in selecting patients for acute stroke therapy. Understanding the use of these imaging modalities and techniques in dealing with an emergency such as acute stroke has therefore become more important than ever for physicians treating patients with acute stroke.

SUMMARY:
Imaging the brain and the blood vessels supplying it using modern tools and techniques is a key step in understanding the pathophysiology of acute stroke and making appropriate and timely clinical decisions.

KEY POINTS
- As time is of the essence in the management of patients with acute stroke, clinical assessment and imaging interpretation must happen quickly.
- Imaging is used in acute stroke to help determine diagnosis, prognosis, and appropriate treatment selection.
- CT is the workhorse of acute stroke imaging because of its speed and ease of acquisition, 24/7 availability, lower cost, and relative absence of contraindications when compared to MRI.
- The primary purpose of noncontrast CT in patients with acute stroke is to rule out a hemorrhagic stroke and to identify imaging features that may suggest the presence of an ischemic stroke.
- The classic radiologic signs of early ischemic change seen on noncontrast CT are obscuration of the lentiform nucleus, the insular ribbon sign (loss of gray-white matter differentiation at the insula), and the cortical ribbon sign (loss of gray-white matter differentiation at the surface cortex).
- The two most widely used methods to assess the extent of early ischemic changes in brain supplied by the middle cerebral artery are the one-third middle cerebral artery rule and the Alberta Stroke Program Early CT Score (ASPECTS).
- On noncontrast CT, brain regions that are darker than the contralateral normal-appearing white matter are a marker of increased risk of hemorrhage with thrombolysis. The presence of these regions does not mean that thrombolysis is absolutely contraindicated, but they do mean that clinicians should proceed with caution after weighing the risks and benefits of thrombolysis.
- The primary modality used to image blood vessels supplying the brain is CT angiography (CTA). It is best to acquire a head and neck CTA (aortic arch to vertex) to visualize all extracranial and intracranial arteries supplying the brain.
- CTA is a useful tool to help understand the etiology of any intracranial hemorrhage and to identify underlying pathologies, such as intracranial aneurysms, arteriovenous malformations, dural arteriovenous fistulas, and any other vascular malformations.
- On CTA, the spot sign is a serpiginous or linear contrast density located within the parenchymal hemorrhage. The presence of a spot sign suggests hemorrhage that is likely to grow over time.
- CTA is an essential tool in the management of patients with acute ischemic stroke. It helps in detecting thrombi within arteries and their extent, collateral status beyond occlusive thrombus, and any other associated pathologies. The tool also helps in determining the risk of recurrent strokes and in planning acute endovascular treatment and surgical management of carotid stenosis.
- Multiphase CTA is an excellent tool to assess collateral status. On the three time-resolved phases of the multiphase CTA, arteries distal to the blocked artery are assessed for extent of arterial contrast, delay in filling of contrast, and impaired washout of contrast when compared to arteries on the contralateral side.
- Head and neck CTA is an important tool in planning acute endovascular thrombectomy. Assessment of the aortic arch and large artery anatomy helps in choosing the type of catheter to be used during the procedure. In addition, the location and extent of thrombus within the arterial tree also helps determine the device type and profile used for mechanical thrombectomy.
CT perfusion (CTP) involves acquiring multiple scans of the brain over time; summing these time-resolved images of contrast filling in and washing out from brain using mathematical formulas; and generating estimates of cerebral blood flow, blood volume, and transit time within brain tissue.

- Current CTP techniques are prediction tools. They help predict the probability of brain tissue being dead or alive by estimating the degree of blood flow within that tissue.
- Brain tissue with very low blood flow on CTP is likely to infarct early. By detecting regions of very low blood flow (or blood volume) or regions of brain with increased blood-brain barrier permeability, CTP can help predict brain regions with increased risk of hemorrhage after acute stroke treatment.
- Subacute-appearing changes on noncontrast CT or regions of the brain with changes seen on diffusion-weighted images (DWI) and fluid-attenuated inversion recovery (FLAIR) images (no DWI-FLAIR mismatch) may also help clinicians predict the risk of hemorrhage with acute treatment.

**Article 4: Endovascular Treatment of Acute Ischemic Stroke**


**ABSTRACT**

**PURPOSE OF REVIEW:**
This article reviews the actual indications for mechanical thrombectomy in patients with acute ischemic stroke and how the opportunities for endovascular therapy can be expanded by using the concept of clinical-imaging or perfusion-imaging mismatch (as a surrogate for salvageable tissue) rather than time of ischemia.

**RECENT FINDINGS:**
Six randomized controlled trials undoubtedly confirmed the benefits of using endovascular thrombectomy on the clinical outcome of patients with stroke with large vessel occlusion within 6 hours from symptom onset compared with those receiving only standard medical care. In a meta-analysis of individual patient data, the number needed to treat with endovascular thrombectomy to reduce disability by at least one level on the modified Rankin Scale for one patient was 2.6. Recently, the concept of “tissue window” versus time window has proved useful for selecting patients for mechanical thrombectomy up to 24 hours from symptom onset. The DAWN (DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention) trial included patients at a median of 12.5 hours from onset and showed the largest effect in functional outcome ever described in any acute stroke treatment trial (35.5% increase in functional independence). In DEFUSE 3 (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution 3), patients treated with mechanical thrombectomy at a median of 11 hours after onset had a 28% increase in functional independence and an additional 20% absolute reduction in death or severe disability.

**SUMMARY:**
For patients with acute ischemic stroke and a large vessel occlusion in the proximal anterior circulation who can be treated within 6 hours of stroke symptom onset, mechanical thrombectomy with a second-generation stent retriever or a catheter aspiration device should be indicated regardless of whether the patient received treatment with intravenous (IV) recombinant tissue plasminogen activator (rtPA) in patients with limited signs of early ischemic changes on neuroimaging. Two clinical trials completely disrupted the time window concept in
acute ischemic stroke, showing excellent clinical outcomes in patients treated up to 24 hours from symptom onset. Time of ischemia is, on average, a good biomarker for tissue viability; however, the window of opportunity for treatment varies across different individuals because of a range of compensatory mechanisms. Adjusting time to the adequacy of collateral flow leads to the concept of tissue window, a paradigm shift in stroke reperfusion therapy.

**KEY POINTS**

- Although IV recombinant tissue plasminogen activator (rtPA) is safe and effective in reducing disability in patients with acute ischemic stroke, several limitations prevent its more widespread use, including its narrow therapeutic time window and poor effect in the recanalization of large vessels.
- An essential premise in the development and optimization of endovascular therapies for acute ischemic stroke is the notion of the ischemic penumbra, essentially described as the area of brain tissue that is still viable but is critically hypoperfused and will progress to infarct in the absence of timely reperfusion.
- The different behaviors relative to the time–ischemia construct are now better delineated, allowing for the possibility of improving the selection of patients for acute reperfusion therapies.
- The duration of the penumbra in humans varies substantially, depending on factors such as degree of collateral blood flow supply, cerebral perfusion pressure, susceptibility of tissue to ischemia and ischemic preconditioning, location of the vessel occlusion, and other specific factors such as hyperglycemia, body temperature, and oxygen delivery capacity.
- In patients with proximal cerebral artery occlusions, no single practical and reliable imaging biomarker predicts infarct growth into the surrounding penumbra; however, the principles of clinical-imaging mismatch and perfusion-imaging mismatch have revolutionized the evaluation of patients with acute ischemic stroke.
- Cerebral collaterals can be broadly divided into the short bypass segments at the circle of Willis and the elongated leptomeningeal anastomotic routes able to deliver retrograde perfusion to adjacent vascular territories.
- The natural history of proximal intracranial arterial occlusion is usually that of poor outcomes. However, clinical severity at presentation (eg, baseline National Institutes of Health Stroke Scale [NIHSS] score) and the presence of collateral flow seem to be more important than the level of proximal intracranial arterial occlusion in determining the prognosis.
- An accurate assessment of the cerebral collateral circulation is a very important prerequisite for the appropriate management of patients with acute ischemic stroke.
- The success of the pivotal clinical trials demonstrating the efficacy of endovascular stroke therapy is mostly attributable to the use of next-generation mechanical thrombectomy devices, resulting in better recanalization rates, and to more rigid neuroimaging criteria for the choice of endovascular treatment candidates.
- CT perfusion might be helpful in choosing patients with higher chances of benefiting from the treatment. However, clinicians should be aware that CT perfusion may cause significant delays in workflow due to the longer acquisition and processing times, and it does not invariably provide accurate information, resulting in both overestimation and underestimation of ischemic core.
- Several studies have shown that automated processing of CT perfusion and MRI can provide a quantitative mismatch classification even among inexperienced neuroimaging centers.
- Recently, two clinical trials completely disrupted the time window concept in acute ischemic stroke, showing excellent clinical outcomes in patients treated up to 24 hours from symptom onset; effectiveness of late-window thrombectomy was maintained across all subgroups, including those defined by time, age, mode of presentation, and the Alberta Stroke Program Early CT Score (ASPECTS).
- Outcomes after mechanical thrombectomy seem to depend on the interaction of several variables including infarct volume, regional eloquence, age, and baseline functional status.
- The safety profile in the late time window seems to be similar to mechanical thrombectomy performed in up to 6 hours from symptom onset.
Article 5: Cerebral Small Vessel Disease

Natalia S. Rost, MD, MPH, FAAN, FAHA; Mark Etherton, MD, PhD. Continuum (Minneap Minn). April 2020; 26 (2 Cerebrovascular Disease):332–352.

ABSTRACT

PURPOSE OF REVIEW:
This article reviews the clinical significance and neuroimaging characteristics of cerebral small vessel disease and the impact on neurologic disease and current and potential therapeutic approaches.

RECENT FINDINGS:
Cerebral small vessel disease is increasingly prevalent and highly heterogeneous in neuroimaging and clinical presentation. Small subcortical infarcts, lacunes, cerebral microbleeds, cortical microinfarcts, and white matter hyperintensity of presumed vascular origin represent the major neuroimaging markers of small vessel disease. Increasing small vessel disease burden is associated with risk of incident stroke and dementia, as well as other neuropsychiatric symptoms. Current research strategies are targeting elucidation of the mechanisms of small vessel disease pathogenesis and pursuing clinical trials of therapeutic agents to reduce the clinical manifestations of cerebral small vessel disease.

SUMMARY:
Cerebral small vessel disease is common in aging adults and represents a major risk factor for multiple acute and chronic neurologic diseases. Increased awareness of cerebral small vessel disease as a modifiable risk factor holds potential for reducing neurologic disease morbidity and mortality across diverse populations in the United States and worldwide.

KEY POINTS
- Small vessel disease is prevalent among healthy aging adults and patients diagnosed with acute ischemic stroke or intraparenchymal hemorrhage.
- Small vessel disease is a multifaceted cerebrovascular syndrome that is composed of distinct clinical, neuropathologic, and neuroimaging findings.
- Brain MRI plays an essential role in the diagnosis and characterization of the small vessel disease spectrum.
- White matter hyperintensity is known to be one of the most well-characterized features of the small vessel disease neuroimaging spectrum; it is a validated biomarker and an established risk factor for stroke and intraparenchymal hemorrhage (incident and recurrent), vascular cognitive impairment and dementia, mortality, and functional disability among healthy aging adults and in patients with acute ischemic stroke.
- In cerebral amyloid angiopathy, several hemorrhagic manifestations, including acute intraparenchymal hemorrhage, subclinical macrohemorrhages, cerebral microbleeds, cortical subarachnoid hemorrhage, and cortical superficial siderosis, have been described.
- Cortical microinfarcts are silent and usually undetectable on conventional neuroimages.
- Small vessel disease is the most common cause of vascular cognitive impairment and dementia.
- Small vessel disease represents a significant risk factor for ischemic stroke, specifically small vessel occlusive mediated infarcts (lacunar stroke), and hemorrhagic stroke.
- In adults older than 55 years of age, cerebral amyloid angiopathy represents the most common etiology of spontaneous, nontraumatic lobar intraparenchymal hemorrhage.
- Apathy, depression, parkinsonism, anxiety, hallucinations, and sleep disturbances have all been reported in patients with small vessel disease.
- Intensive treatment of hypertension seems promising for treatment of small vessel disease.
Given the multifactorial benefits of smoking cessation, diet, and aerobic exercise in secondary stroke prevention, these lifestyle modifications should be emphasized in all patients with stroke regardless of small vessel disease burden.

Article 6: The Evolving Concept of Cryptogenic Stroke


ABSTRACT

PURPOSE OF REVIEW:
This article discusses cryptogenic stroke and the results of recent randomized trials that can inform its evaluation and management.

RECENT FINDINGS:
Most cryptogenic strokes appear embolic, leading to the term embolic stroke of undetermined source. It was previously thought that embolic stroke of undetermined source was a single, therapeutically relevant entity, the underlying sources of which would respond to anticoagulant therapy; however, two large randomized trials found no benefit with anticoagulation compared to antiplatelet therapy for secondary stroke prevention after embolic stroke of undetermined source. A single antiplatelet drug remains the recommended long-term antithrombotic treatment for secondary stroke prevention in embolic stroke of undetermined source. However, three caveats should be considered with regard to cryptogenic stroke. First, those with minor stroke symptoms presenting early after onset should receive 3 weeks of dual antiplatelet therapy. Second, all patients with cryptogenic stroke should be monitored for atrial fibrillation. Third, patients 60 years of age or younger with a patent foramen ovale (PFO) should be carefully evaluated to determine whether the PFO may have caused the stroke and whether they might benefit from PFO closure.

SUMMARY:
More personalized strategies may soon be available to guide treatment of cryptogenic stroke. In the meantime, it is hoped that the application of recent findings from clinical trials will reduce stroke recurrence in this important population.

KEY POINTS
- It is important to elucidate the underlying mechanism of stroke because such knowledge informs treatment to prevent recurrent stroke.
- About one-fourth of ischemic strokes are cryptogenic, and one-sixth meet the definition of embolic stroke of undetermined source.
- The minimum evaluation of ischemic stroke involves a transthoracic echocardiogram, imaging of the cervical and intracranial arteries, a 12-lead ECG, and at least 24 hours of continuous heart-rhythm monitoring.
- Based on two high-quality randomized clinical trials, it is clear that an empiric strategy of anticoagulation for all cases of cryptogenic stroke is not effective and may be harmful. Therefore, a single antiplatelet agent remains the recommended long-term antithrombotic treatment for secondary stroke prevention.
- Patients with cryptogenic stroke with minor stroke symptoms presenting early after onset should be treated with a 3-week course of dual antiplatelet therapy.
- Patients with cryptogenic stroke should be monitored for atrial fibrillation.
Patients with cryptogenic stroke with a patent foramen ovale (PFO) should be carefully evaluated to determine whether the PFO may have been responsible for the stroke and whether they might benefit from PFO closure.

**Article 7: Stroke in Women**

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**ABSTRACT**

**PURPOSE OF REVIEW:**
This article reviews sex differences in stroke risk and presentation, with a particular emphasis on the unique risk factors women experience throughout the lifespan.

**RECENT FINDINGS:**
Although prior studies suggested women have worse outcomes after stroke, it is now clear that age, prestroke functional status, and comorbidities explain many of the differences between men and women in stroke severity, functional outcomes, and mortality. Several meta-analyses and large cohort studies have evaluated the risk factors for women related to reproductive factors and found that fewer years between menarche and menopause, pregnancy complications (preeclampsia/eclampsia, preterm delivery, and stillbirth), oophorectomy, hormone replacement therapy use, and younger age at menopause all increase the risk of stroke. Although the nonreproductive risks of stroke overlap between men and women, those with greater impact on women include age, hypertension, atrial fibrillation, socioeconomic status, and depression.

**SUMMARY:**
Significant sex differences are observed in risk factors of stroke and stroke outcome. Including this information in the clinical assessment of the individual patient may support development of more effective prevention plans.

**KEY POINTS**
- Although the incidence of stroke up to 2010 appeared to be decreasing overall, this trend is driven by a decrease in incidence in men, not women.
- Age at menarche at 10 years of age or younger increases the risk of stroke later in life by about 25%.
- Women with preeclampsia have an increased risk of both ischemic and hemorrhagic stroke in the peripartum and postpartum periods, and this risk increases with additional comorbidities such as atrial fibrillation, migraine, or congenital heart disease.
- Pregnant women with an acute stroke may be candidates for either IV thrombolysis or thrombectomy; referral to a center with multidisciplinary expertise is essential for these treatment decisions.
- Hypertensive disorders of pregnancy increase the risk of multiple vascular complications later in life, including hypertension, stroke, heart disease, heart failure, and cerebral microvascular disease.
- A reproductive lifespan of less than 30 years (age of menarche subtracted from the age at menopause) is associated with an increased risk of stroke.
- Women have strokes at older ages and tend to have lower levels of education than men, so it is important to tailor necessary resources accordingly.
- Compared to men, women have a higher prevalence of hypertension over age 65, and women with stroke are more likely to have hypertension, probably due to older age of stroke onset.
Atrial fibrillation has a higher impact on the risk of stroke in women compared to men. This can be explained by the more advanced age in women at the time of stroke, that atrial fibrillation carries twice the risk of stroke in women in comparison to men, and, further, women have more severe stroke presentations than men in stroke related to atrial fibrillation.

- Women are more likely to present with nontraditional stroke symptoms and mimics than men.
- Women have worse outcomes after stroke than men, a result of older age at the time of stroke onset, worse prestroke functional status, and multiple comorbidities in women.
- Women are underrepresented in many clinical trials of stroke treatments, limiting the full understanding of both benefits and harm in women.

Article 8: Ischemic Stroke in Young Adults

Jukka Putaala, MD, PhD, MSc. Continuum (Minneap Minn). April 2020; 26 (2 Cerebrovascular Disease):386–414.

ABSTRACT

PURPOSE OF REVIEW:
This article reviews current knowledge on epidemiology, risk factors and causes, diagnostic considerations, management, and prognosis of ischemic stroke in young adults (those 55 years old and younger).

RECENT FINDINGS:
The incidence of ischemic stroke in young adults has been increasing since the 1980s, which has occurred in parallel with increasing prevalence of vascular risk factors and substance abuse among the younger population. Young adults have a considerably wider range of risk factors than older patients, including age-specific factors such as pregnancy/puerperium and oral contraceptive use. Behavioral risk factors such as low physical activity, excess alcohol consumption, and smoking are factors as well. More than 150 identified causes of early-onset ischemic stroke exist, including rare monogenic disorders. Several recent advances have been made in diagnosis and management of stroke in young adults, including molecular characterization of monogenic vasculitis due to deficiency of adenosine deaminase 2 and transcatheter closure of patent foramen ovale for secondary prevention. Compared with the background population of the same age and sex, long-term mortality in patients remains fourfold higher with cardiovascular causes underlying most of the deaths. The cumulative rate of recurrent stroke extends up to 15% at 10 years. Patients with atherosclerosis, high-risk sources of cardioembolism, and small vessel disease underlying their stroke seem to have the worst prognosis regarding survival and recurrent vascular events. Young stroke survivors also often have other adverse outcomes in the long term, including epilepsy, pain, cognitive problems, and depression.

SUMMARY:
Systematic identification of risk factors and causes and the motivation of patients for long-term prevention and lifestyle changes are of utmost importance to improve the prognosis of early-onset ischemic stroke.

KEY POINTS
- Of great public health importance, the incidence of ischemic stroke at younger ages has been increasing worldwide from the 1980s to 2010s.
In the large Stroke in Young Fabry Patients study, the most common risk factors were abdominal obesity, tobacco smoking, physical inactivity, and hypertension.

Migraine with aura is a risk factor for early-onset ischemic stroke.

The risk for ischemic stroke or myocardial infarction increases with higher doses of estrogen and is doubled for women taking pills containing at least 50 mcg of estrogen compared with nonusers.

Ischemic stroke complicates fewer than 20 per 100,000 pregnancies. The risk is highest during the third trimester, around delivery, and in the postpartum period.

The association of patent foramen ovale and ischemic stroke appears stronger for younger (approximately fivefold risk) than older individuals (approximately twofold risk) when compared with stroke-free individuals or patients with known stroke causes.

The Risk of Paradoxical Embolism (RoPE) score may be helpful when estimating the probability of a patent foramen ovale causing the stroke. In the RoPE score, younger age, cortical infarct, and a lack of vascular risk factors give more points and a greater probability of stroke-related patent foramen ovale.

Both recent and long-term heavy drinking, including binge drinking, have been shown to increase the risk of ischemic stroke at younger ages.

The route and mode of illicit drug administration modulate the risk and affect the possible pathophysiologic mechanisms of ischemic stroke.

Malignancy is a risk factor for ischemic stroke in young adults.

Antiphospholipid syndrome can be diagnosed with two positive blood test results at least 12 weeks apart showing the presence of antiphospholipid antibodies—most commonly lupus anticoagulant, antiphospholipid antibodies, or anti–β2 glycoprotein-I antibodies—reacting against proteins that bind to phospholipids on plasma membranes.

In most young patients with ischemic stroke, anticardiolipin antibodies or anti–β2 glycoprotein-I antibodies are only modestly elevated, and often on one occasion only, and so criteria for antiphospholipid syndrome are not met.

Rare causes, eg, noninflammatory and inflammatory vasculopathies, hematologic causes, and monogenic disorders, together cause up to 22% of ischemic strokes in young adults.

The most frequent singular cause of ischemic stroke in young adults is carotid artery dissection, causing up to one-fifth of all events. In the largest series, etiology of stroke remained undetermined in up to 40%.

One recent finding in young patients with otherwise cryptogenic stroke is the presence of carotid webs, which are seen on CT angiography and defined as intimal variants of fibromuscular dysplasia appearing as a shelflike lesion on the posterior aspect of the carotid bulb.

A routine 12-lead ECG is a first-line investigation that can reveal occult atrial fibrillation and hints from other high-risk sources of embolism. For example, P terminal force in lead V1 appeared strongly associated with a final diagnosis of cardioembolism in young patients.

Cardiac MRI and CT can be used as complementary studies, especially when further information is needed on intracardiac masses, congenital heart disease, valvular disease, or when transesophageal echocardiography is contraindicated or resulted in suboptimal findings.

Discontinuation of antiplatelets and antihypertensives and poor adherence to antihypertensives are associated with a heightened risk of recurrent stroke, other vascular events, and mortality.

Three positive trials compared transcatheter closure of patent foramen ovale with medical treatment. A meta-analysis of these and two earlier completed trials concluded that patent foramen ovale closure reduces the risk of recurrent ischemic stroke with an odds ratio of 0.43 (95% CI, 0.21 to 0.90) and a number needed to treat of 46. However, a significant increase in new-onset atrial fibrillation was associated with transcatheter closure with an odds ratio of 5.15 (95% CI, 2.18 to 2.15), although atrial fibrillation episodes in most patients may have been transient.

In carotid artery dissection, a randomized trial found no difference between antiplatelets and anticoagulants in prevention of recurrent stroke.

The risk of recurrence remains high for years after the index ischemic event, with cumulative risk for stroke around 10% at 5 years and 15% at 10 years.
- One study followed young patients with ischemic stroke and transient ischemic attack and age-matched controls for 11 years and observed that up to 50% of the patients had a decline in their cognitive skills even if the motor symptoms were mild.
- A substantial proportion of young patients with ischemic stroke are not able to return to work, and this proportion increases over time.

Article 9: Recovery After Stroke


ABSTRACT

PURPOSE OF REVIEW: This article describes restorative therapies to improve patient outcomes after stroke. These therapies contrast with acute stroke treatments such as recombinant tissue plasminogen activator (rtPA) and thrombectomy that target clots, aim to salvage threatened brain tissue to limit injury, and have a time window measured in hours. Restorative therapies target the brain, aim to promote plasticity within surviving brain tissue, and have a time window measured in days to weeks or longer.

RECENT FINDINGS: A number of drugs are under study. Preclinical studies are providing attractive therapeutic candidates for translation, such as the C-C chemokine receptor 5 inhibitor maraviroc. Some drug studies have used a pragmatic approach, which is premature for the nascent field of neural repair. Substantial data support the utility of activity-dependent therapies, including constraint-induced movement therapy, with recent studies supporting the need for very high doses to generate the best functional gains. While stem cell therapies are at an early stage, mounting preclinical evidence supports the efficacy of mesenchymal stem cells; some initial human studies are supportive. Several types of brain stimulation have been examined, and in some cases initial studies are promising.

SUMMARY: Improved insights into stroke recovery and its treatment have the potential to reduce disability in a large segment of stroke survivors.

KEY POINTS
- A stroke also triggers numerous cellular and molecular cascades that facilitate spontaneous repair and recovery.
- In contrast to acute stroke treatments such as recombinant tissue plasminogen activator (rtPA) and thrombectomy, recovery treatments target surviving brain tissue with the goal of promoting neural repair.
- Evidence exists that a very high dose of rehabilitation therapy results in large improvements in functional status.
- The physiologic state of the brain evolves rapidly and substantially during the weeks that follow a stroke, and this carries with it varying receptivity and vulnerability to interventions at different time points during this period.
- As with all restorative therapies, studying the mechanism of action in humans will increase the likelihood that the target population can be identified and that methods can be devised to stratify patients according to the likelihood that treatment will provide benefit.
- Therapeutic targets of stroke recovery vary over time.
Increasing evidence suggests that the best results derived from a restorative therapy occur when the therapy is paired with concomitant training.

It is useful to understand the sites of brain injury and details of brain function perturbation that have occurred consequent to the infarct to optimize clinically useful neural plasticity.

When treating the brain after stroke to promote neural plasticity, treatment will be maximally effective when patients are stratified on the basis of assessments that identify target patient subgroups.

Restorative therapies benefit patients by improving the function of specific neural systems. Improvement is seen in neural systems with sufficient surviving substrate that are amenable to repair.

**Article 10: Medical Management for Secondary Stroke Prevention**


**ABSTRACT**

**PURPOSE OF REVIEW:**
This article reviews the evidence base and recommendations for medical management for secondary stroke prevention.

**RECENT FINDINGS:**
Recent developments for secondary stroke prevention include evidence to support the use of short-term dual antiplatelet therapy after minor stroke and transient ischemic attack, direct oral anticoagulants for nonvalvular atrial fibrillation, reversal agents for direct oral anticoagulant–associated hemorrhage, and aspirin rather than presumptive anticoagulation with a direct oral anticoagulant for embolic stroke of undetermined source.

**SUMMARY:**
Most strokes are preventable. The mainstays of medical management for secondary stroke prevention include antihypertensive therapy; antithrombotic therapy, with antiplatelet agents for most stroke subtypes or anticoagulants such as warfarin or a direct oral anticoagulant for cardioembolic stroke specifically; cholesterol-lowering therapy, principally with statins, but with potential roles for ezetimibe or proprotein convertase subtilisin/kexin type 9 inhibitors in selected patients; and glycemic control to prevent microvascular complications from diabetes mellitus or pioglitazone in selected patients with insulin resistance but not diabetes mellitus.

**KEY POINTS**
- Prevention of recurrent stroke requires an early and aggressive approach.
- Most strokes are preventable.
- Medical management is but one component of a comprehensive approach to stroke secondary prevention that may include surgical or procedural options, behavioral interventions, and addressing the social determinants of health.
- The choice of antihypertensive agents used should be individualized with a focus on the degree of blood pressure reduction achieved.
- For secondary stroke prevention, a blood pressure target of <140/90 mm Hg is justified, and a more stringent goal of <130/80 mm Hg is reasonable for selected patients.
- Aspirin 325 mg should be administered initially for most patients with stroke or transient ischemic attack.
A loading dose of clopidogrel followed by 21 days of treatment with aspirin and clopidogrel is reasonable when initiated up to 3 days after minor stroke and transient ischemic attack.

Chronic use of combination aspirin and clopidogrel therapy is not recommended for stroke secondary prevention.

Triple antiplatelet therapy with aspirin, clopidogrel, and dipyridamole for secondary stroke prevention is not recommended.

Cilostazol and ticagrelor are investigational antiplatelet agents, and their precise role in treatment of stroke is unclear.

Anticoagulation with warfarin or direct oral anticoagulants is indicated for secondary stroke prevention for cardioembolic stroke including nonvalvular atrial fibrillation and valvular heart disease.

Statins are a first-line treatment for dyslipidemia after stroke.

Ezetimibe can be considered with statin intolerance or when the response to statins is inadequate.

Proprotein convertase subtilisin/kexin type 9 inhibitors can result in dramatic reductions of low-density lipoprotein levels but are costly and require subcutaneous injections.

Intensive glycemic control may have benefits for microvascular disease, but intensive management of glucose levels after acute stroke or for chronic secondary stroke prevention may have limited benefits over standard therapy.

Pioglitazone may have benefits for secondary prevention in patients with documented insulin resistance, but this is partially outweighed by adverse events.

### Article 11: Surgical Approaches to Stroke Risk Reduction


**ABSTRACT**

**PURPOSE OF REVIEW:** Surgical vascular intervention is an important tool in reducing the risk of stroke. This article examines the evidence for using the available options.

**RECENT FINDINGS:** Carotid endarterectomy is an effective treatment option for reducing the risk of stroke in appropriately selected patients. Patients should be stratified for future stroke risk based on both the degree of stenosis and the presence of symptoms referable to the culprit lesion. Carotid stenting is also useful in reducing stroke risk, again in carefully selected patients. Because of the publication of significant data regarding both carotid endarterectomy and carotid artery stenting in the last several years, selection can be far more personalized and refined for individual patients based on demographics, sex, patient preference, and medical comorbidities. Routine extracranial-intracranial bypass surgery remains unproven as a therapeutic option for large vessel occlusion in reducing the incidence of ischemic stroke although some carefully screened patient populations remaining at high risk may benefit; procedural risks and pathology related to alterations in blood flow dynamics are challenges to overcome. Indirect revascularization remains an appropriate solution for carefully selected patients with cerebral large vessel steno-occlusive disease, and multiple variations of surgical technique are patient specific. Indirect revascularization may benefit from clinical trials with larger patient populations for validation in specific pathologies and offers the advantages of lower surgical complication rates and reduced risk of pathologic responses to altered cerebral flow dynamics.
SUMMARY:
Surgical solutions to reduce stroke risk provide important alternatives in appropriately selected
patients and should be considered in addition to medical management and lifestyle modification
for optimizing patient outcomes.

KEY POINTS

- In select patients, carotid endarterectomy remains an effective and durable solution to reducing the risk of
  stroke.
- For optimal care, patients should be risk stratified by both the degree of carotid stenosis and symptomatic
  status.
- Carotid artery stenting is an appropriate alternative to endarterectomy in a subset of patients, depending on
certain aspects of the patient’s overall health and demographic profile.
- Patients presenting with asymptomatic internal artery stenosis greater than 70% should be referred for
  potential enrollment into the CREST-2 clinical trial.
- Intensive medical management remains an important adjuvant for stroke risk reduction irrespective of the
decision regarding surgical risk reduction with revascularization by either carotid endarterectomy or carotid
artery stenting procedures.
- Multiple large, multicenter trials comparing surgical with medical management have failed to demonstrate an
  advantage for surgical revascularization in patients with symptomatic, intracranial steno-occlusive arterial
disease. Routine extracranial-intracranial bypass surgery remains unproven as a therapeutic option for large
vessel occlusion in reducing the incidence of ischemic strokes, although some carefully screened patient
populations remaining at high risk may benefit.
- The majority of risk in extracranial-intracranial bypass surgeries is immediate to the periprocedural
timeframe and not secondary to patency failure of the revascularization bypass.
- Patients with refractory, symptomatic, intracranial steno-occlusive arterial disease and ongoing ischemic
  events, who are carefully selected with multimodal diagnostic testing, may benefit from surgical
revascularization.
- Intensive medical management remains an important adjuvant for risk reduction in patients with
  symptomatic, intracranial steno-occlusive arterial disease.
- Indirect surgical revascularization may represent an appropriate alternative to reduce the incidence of stroke
  in patients with symptomatic intracranial atherosclerotic disease.
- Randomized clinical trials are needed to validate the appropriateness and efficacy of indirect
  revascularization in mitigating stroke risk in patients with symptomatic intracranial atherosclerotic disease.

Article 12: Management of Unruptured Cerebral Aneurysms and Arteriovenous Malformations


ABSTRACT

PURPOSE OF REVIEW:
Unruptured intracranial aneurysms and brain arteriovenous malformations (AVMs) may be
detected as incidental findings on cranial imaging. This article provides a practical approach to
the management of unruptured intracranial aneurysms and unruptured brain AVMs and reviews
the risk of rupture, risk factors for rupture, preventive treatment options with their associated risks, and the approach of treatment versus observation for both types of vascular malformations.

RECENT FINDINGS:
For unruptured intracranial aneurysms, scoring systems on the risk of rupture can help with choosing preventive treatment or observation with follow-up imaging. Although the literature provides detailed information on the complication risks of preventive treatment of unruptured intracranial aneurysms, individualized predictions of these procedural complication risks are not yet available. With observation with imaging, growth of unruptured intracranial aneurysms can be monitored, and prediction scores for growth can help determine the optimal timing of monitoring. The past years have revealed more about the risk of complications of the different treatment modalities for brain AVMs. A randomized clinical trial and prospective follow-up data have shown that preventive interventional therapy in patients with brain AVMs is associated with a higher rate of neurologic morbidity and mortality compared with observation.

SUMMARY:
The risk of hemorrhage from both unruptured intracranial aneurysms and brain AVMs varies depending on the number of risk factors associated with hemorrhage. For both types of vascular malformations, different preventive treatment options are available, and all carry risks of complications. For unruptured intracranial aneurysms, the consideration of preventive treatment versus observation is complex, and several factors should be included in the decision making. Overall, it is recommended that patients with unruptured asymptomatic brain AVMs should be observed.

KEY POINTS
- Rupture of an aneurysm leads to a subarachnoid hemorrhage, which has devastating effects; one-third of patients die, and one-third are rendered dependent.
- The PHASES (Population, Hypertension, Age, Size of aneurysm, Earlier subarachnoid hemorrhage from another aneurysm, and Site of aneurysm) score provides absolute estimates for the 5-year risk of rupture of unruptured intracranial aneurysms based on the presence of these different risk factors.
- Depending on the number of different risk factors present, the 5-year risk of rupture of unruptured intracranial aneurysms ranges from 0.25% to more than 15%.
- Patient-related risk factors for rupture of unruptured intracranial aneurysms in addition to the PHASES score are smoking and, possibly, a positive family history of intracranial aneurysms.
- In addition to the PHASES score, aneurysm-related risk factors for unruptured intracranial aneurysm rupture are irregular shape and possibly aspect ratio (the ratio of aneurysm neck-to-dome length to aneurysm neck width) and height to width ratio.
- Unruptured intracranial aneurysms can be preventively treated by surgical clipping or endovascular coilig. Both treatments have a risk of complications, and different factors associated with an increased risk have been identified.
- When deciding whether to preventively treat unruptured intracranial aneurysms, several factors should be considered, including the life expectancy of the patient, the estimated risk of rupture, the risk of complications of preventive treatment, and the level of anxiety of the patient with regard to the knowledge of having an unruptured intracranial aneurysm.
- If an unruptured intracranial aneurysm is not preventively treated by surgery or endovascular treatment, patients are often advised to undergo serial follow-up imaging to detect aneurysm growth.
- The risk of rupture of unruptured intracranial aneurysms that grew during follow-up is higher than in unruptured intracranial aneurysms that remained stable. In the case of growth, the decision not to preventively treat the unruptured intracranial aneurysm should be reconsidered.
- Hypertension should be treated in patients with an unruptured intracranial aneurysm, and these patients should be advised to quit smoking.
- The mortality rate after hemorrhage from a brain arteriovenous malformation has a wide range from 12% to 67%, and, of the patients who survive the hemorrhage, approximately 45% have severe deficits.
- The risk of hemorrhage from a previously unruptured brain arteriovenous malformation is 1% to 3% per year, and the risk varies depending on the number of risk factors associated with brain arteriovenous malformation hemorrhage.
- Risk factors associated with brain arteriovenous malformation hemorrhage are previous hemorrhage, race, age, deep brain location, and exclusive deep venous drainage.
- Brain arteriovenous malformations can be preventively treated by microsurgery, endovascular embolization, and stereotactic radiosurgery. Each treatment has a risk of complications, and different factors associated with an increased risk have been identified.
- The main goal of treatment is to prevent hemorrhage from the brain arteriovenous malformation, but treatment to control seizures or stabilization of progressive neurologic deficits caused by the brain arteriovenous malformation may also be considered.
- Microsurgery, endovascular embolization, and stereotactic radiosurgery are often combined to optimally treat brain arteriovenous malformations.
- Follow-up imaging can take place after treatment of a brain arteriovenous malformation to ensure that it is completely obliterated. This imaging is certainly indicated after embolization and radiosurgery.
- Patients with brain arteriovenous malformations have a higher rate of neurologic morbidity and mortality after preventive interventional therapy compared with observation. These data indicate that patients with unruptured asymptomatic brain arteriovenous malformations should be observed. However, in the case of unruptured symptomatic arteriovenous malformations, treatment may be considered to reduce epileptic seizures or neurologic deficits caused by the arteriovenous malformations.
- Evidence to support the use of imaging to screen and monitor patients with unruptured brain arteriovenous malformations is lacking.
- No medical treatment is available to treat brain arteriovenous malformations or to reduce the risk of hemorrhage from them.