highest recurrence risk underscores the need for urgent evaluation and implementation of therapeutic and preventive strategies after a TIA or minor stroke.

STROKE SUBTYPES

Large-vessel, atherothrombotic stroke/TIA subtype Atherothrombotic cerebral vascular disease accounts for approximately 25% of all ischemic strokes. To determine that a stroke is secondary to large-vessel atherosclerotic disease, it is required that the artery supplying the ischemic territory (extra- or intracranial) reveals a degree of vessel lumen stenosis > 50% of the normal lumen. It is divided into two categories according to the site of atherothrombotic involvement:

1. Extracranial atherosclerotic disease (ECAD)
2. Intracranial atherosclerotic disease (ICAD)

When considered as a group, atheromatous process commonly has a predilection for four extra- and intracranial arterial locations (see **Figure 62-2**): (1) the internal carotid artery (ICA) origin, (2) the carotid siphon portion, (3) the middle cerebral artery stem, and (4) the vertebrobasilar junction. Although the origins of the common carotid and vertebral arteries (VA) also are sites of atheromatous disease, they are less often the cause of stroke or TIA. Atherosclerotic narrowing can also involve the proximal intracranial VA and origins of the posterior cerebral arteries (PCAs), but rarely involve the more distal branches of the cerebral and cerebellar arteries. At each of the sites of predilection, several mechanisms are possible and responsible for causing the stroke or TIA: (1) Embolism: thrombus forms on an atherothrombotic plaque and a piece of clot travels distally to occlude a more distal vessel. This is called an “artery-to-artery” embolus. (2) Thrombus propagation: this is less common, but if the thrombus propagates to occlude a distal vessel off the circle of Willis, large strokes can occur. (3) Hypoperfusion: the atherothrombotic process might occlude or narrow the vessel to such a degree that distal flow is diminished and not compensated via collateral flow through the circle of Willis. This low-flow state may result in border-zone infarctions where an area between the middle cerebral artery-anterior cerebral artery (MCA-ACA) or MCA-PCA territories is

affected cortically or in the distal field of the lenticulostriate penetrating arteries, affecting the deep white matter.

In general, both artery-to-artery embolism and low-flow strokes occur when the vessel is narrowed to a degree that decreases pressure across the arterial segment. Low-flow stroke or TIA occurs less often from a cervical lesion because the circle of Willis can usually provide needed distal collateral circulation when a proximal stenosis becomes hemodynamically significant. Low-flow stroke or TIA occurs more often with atheromatous disease in the intracranial vasculature as this compromises the ability of the circle of Willis to provide sufficient collateral flow. In 70% of the population, the circle of Willis is incompetent, with one or more of the connecting arteries atretic or functionally inadequate (see **Figure 62-2**). In this circumstance, low-flow TIA or stroke may arise from atherothrombosis at the ICA origin or in its petrous or siphon portions.

a. ***Atherothrombotic disease of the anterior cerebral circulation (origin of the ICA, its major branches, and the common carotid artery)*** In the anterior circulation, atheroma occurs most often at the bifurcation of the common carotid artery (CCA), and usually begins on the posterior wall of the ICA origin.
   - *Internal carotid artery*: Most often, atheroma at the origin of the ICA becomes symptomatic after it has narrowed the lumen to the point where the pressure begins to drop across the stenosis, allowing both embolic or low-flow ischemic TIA and stroke to occur. Embolism from thrombus forming in an ulcerated plaque may occur at 50% to 70% stenosis, but it is less common, and rarely occurs with lesser degrees of stenosis. Artery-to-artery embolism can also occur if the atheromatous process occludes the ICA origin forming a thrombus at the site. At times, the occluding thrombus may also propagate without embolization, reaching the ophthalmic artery origin and producing monocular blindness, or extending even more distally to the MCA origin and producing a devastating, full-territory stroke.

     Low-flow symptoms caused by ICA origin stenosis are less common than artery-to-artery embolism, and occur only if two conditions exist: (1) the lesion has to be hemodynamically significant, that is, severe enough to provoke a drop in pressure across the lesion, (2) recruitment of the main collateral channels (circle of Willis and

anastomotic connections between the external carotid artery and ophthalmic artery) is inadequate, leading to a low-pressure state either in the MCA or in one or both of the anterior cerebral arteries. If there is ICA occlusion and little distal collateral flow, then a complete middle cerebral syndrome may result. The PCA territory may also be vulnerable to low flow in the setting of carotid disease when this artery arises directly from the ICA, a variant called "fetal PCA" that is estimated to occur in up to 30% of the population. If the circle of Willis is complete, then occlusion of the ICA can be asymptomatic if it does not have an associated embolic or propagated thrombotic component.

The signs and symptoms of artery-to-artery embolism from the ICA are variable and depend on which intracranial branches are affected. The MCA, receiving majority of the blood flow originating from the ICA will be the most often affected but different symptoms can be the presentation of distal embolization, including from small emboli to the ipsilateral ophthalmic artery. In that case the symptom is called amaurosis fugax, in which a descending shade affecting the ipsilateral eye is usually described by the patient as a brief, usually self-limited phenomenon. In more extreme cases complete and persistent visual loss can occur, usually secondary to a central retinal artery occlusion (CRAO). This constitutes a neuro-ophthalmological emergency and should prompt emergent evaluation for the possibilities of an ipsilateral carotid disease either of atherosclerotic or inflammatory origin (giant cell arteritis [GCA]).

Atheromatous disease in the ICA siphon occurs less often but shares the same type of physiologic mechanisms for TIA and stroke as seen with atheromatous disease of the ICA origin. More proximal involvement, with CCA stenosis or occlusion, is much less common than ICA involvement and can present with similar symptoms.

- *MCA*: MCA territory symptoms can be divided into those involving the stem territory (M1 segment; see **Figure 62-2**) and those involving the superior or inferior territory divisions (M2 segments) or one of their cortical surface branches (see **Figures 62-1** and **62-2**). When the stem of the MCA is occluded (M1 occlusion), a complete MCA syndrome may occur. It produces a complete contralateral hemiplegia and sensory loss involving the face, arm, hand, leg, and foot. Gaze

deviation toward the ischemic hemisphere occurs due to involvement of the frontal eye fields. Ischemia in the dominant hemisphere causes global or partial aphasia and ischemia of the nondominant hemisphere results in neglect (visuospatial and tactile) and anosognosia. The degree of cortical involvement, usually evident clinically by the presence of gaze deviation, aphasia, or neglect, depends on the level of occlusion and the degree of cortical surface collateral flow (see **Figure 62-1**). Smaller emboli cause single superior or inferior branch of the MCA syndromes, or partial branch syndromes. Superior division infarcts, typically present with either isolated contralateral weakness or isolated expressive aphasia or a combination of the two. Inferior division syndromes include difficulty with reading, writing, auditory comprehension of language, or fluent aphasic speech with no limb weakness. Paraphasic errors are common. Neglect of the left visual hemifield and extinction to double tactile stimulation are signs of cortical involvement seen most often in nondominant hemispheric syndromes but may also occur on the right with dominant syndromes.

- *Anterior cerebral artery (ACA)*: ACAs divide into two segments: A1 or stem, a part of the circle of Willis and A2 segment, distal to the anterior communicating artery (see **Figure 62-1**). The A1 segment gives rise to several deep penetrating arteries that supply the anterior limb of the internal capsule, the anterior perforated substance, portions of the anterior hypothalamus, and the posterior part of the head of the caudate nucleus. Infarction in these territories is more often caused by an embolus than by local atheromatous disease. ACA infarcts result predominantly in contralateral leg weakness with varying degrees of contralateral shoulder weakness. If the right and left A2 segments arise from a single anterior cerebral artery A1 segment due to contralateral hypoplastic A1 segment, a normal anatomic variant, an occlusion of this single A1 segment causes bilateral frontal lobe infarction resulting in bilateral leg weakness. Other symptoms of ACA infarcts include urinary incontinence, abulia, gait apraxia, and forced grasping of the hand.
- *Anterior choroidal artery (AChA)*: This artery arises from the ICA and supplies the posterior limb of the internal capsule and its adjacent white matter and medial temporal lobe, also supplying some

geniculocalcarine fibers. The complete clinical syndrome consists of contralateral hemiparesis, hemianesthesia, and hemianopia. However, because this territory is also supplied by penetrating vessels of the MCA stem and the posterior communicating and the posterior choroidal arteries, syndromes with minimal deficits can occur.

b. ***Atherothrombotic disease of the posterior cerebral circulation: vertebrobasilar and posterior cerebral arteries and their branches***

As seen in the anterior circulation, atherosclerosis has a predilection for certain parts of the posterior circulation—namely the proximal origins of the VA, which falls under the category of ECAD, the distal (intracranial) VA, the proximal to mid-basilar artery, and the proximal PCA, which fall under the category of ICAD (see **Figure 62-1**).

- *Vertebral and posterior inferior cerebellar artery*: An occlusion of the distal vertebral or its major branch, the posterior inferior cerebellar artery (PICA), may be caused by either atherothrombosis or by embolism from a proximal arterial source or the heart. VA dissection is another possibility. Atherothrombotic VA stroke is often heralded by TIA or minor stroke. Occlusion of either the VA or the PICA produces infarction in the lateral medulla, resulting in the lateral medullary (Wallenberg) syndrome. The symptoms and signs vary, but more commonly include vertigo, nausea and vomiting, hoarseness, dysphagia, ipsilateral facial numbness associated with impaired sensation of pain and temperature over the ipsilateral face and contralateral arm and leg, ipsilateral Horner syndrome, and ipsilateral limb ataxia. The PICA also supplies the posteroinferior cerebellum that may become infarcted if collateral circulation from the superior cerebellar artery (SCA) is inadequate. The infarct resulting from vertebral occlusion does not differ anatomically from that produced by PICA occlusion, except for a greater involvement of the restiform body (inferior cerebellar peduncle) in the latter. With moderate to large areas of cerebellar infarction, edema might occur and be fatal if not detected early and suboccipital craniectomy performed to relieve the mass effect on the brain stem.
- *Basilar artery*: TIA usually precedes atherothrombotic basilar artery occlusion and the consequent accompanying devastating brain stem infarction. The symptoms of a TIA in the territory of the distal

vertebral and the basilar artery are more varied than in the carotid–middle cerebral territory because of the many different anatomic structures involved. Moreover, brain stem TIAs may be caused by disease of either of the small penetrating branches of the basilar or VA or disease of the basilar or VA themselves. Penetrating branch disease may be due to atherothrombosis, involving the proximal origins of these small branch vessels, or lipohyalinosis, involving the small vessels deeper in the brain stem (see "Lacunar stroke/TIA subtype" later in this chapter). Therefore, when brain stem TIA or acute stroke occurs, it is extremely important to determine whether the problem lies in the basilar artery or in one of its smaller branches. Disease of a basilar branch produces unilateral infarction, whereas disease of the basilar artery itself usually causes bilateral infarction. Transient dizziness associated with diplopia, dysarthria, and numbness around the mouth strongly indicates the presence of basilar insufficiency. Other important symptoms occurring less often include a general profound feeling of weakness of the entire body, staggering, and/or a feeling of propulsion. Bilateral signs such as gaze paresis or internuclear ophthalmoplegia (INO) associated with ipsilateral sensory loss or weakness signify ischemic infarction in both sides of the pons, and therefore exclude single penetrating branch disease as the culprit.

Syndromes of unilateral brain stem infarction typically involve some combination of ipsilateral signs of the head and face, from involvement of cranial nerve nuclei or their fascicles, and contralateral motor and sensory signs in the limbs, from involvement of ipsilateral crossed long tracts, such as the corticospinal tract or spinothalamic tract respectively.

- *Major basilar branches—anterior inferior cerebellar artery (AICA), SCA, PCA*: These major branches of the basilar artery produce their own distinct pathophysiologic syndromes. They are most often caused by artery-to-artery embolism from an atherothrombotic source within the proximal basilar artery or the VA. An aortic or cardiogenic embolic source can be found, especially when the SCA is involved. Rarely, primary atherothrombotic stenosis or occlusion at their origins is the cause of the stroke or TIA.

- *SCA*: Occlusion of the SCA results in one or more of the following symptoms: ipsilateral cerebellar ataxia (caused by ischemia of the middle and/or superior cerebellar peduncle, or dentate nucleus); nausea and vomiting; dysarthria and contralateral loss of pain and temperature sensation over the extremities, body, and face (caused by ischemia of the spinal and trigeminal thalamic tract); and ataxic tremor or choreiform movements of the ipsilateral upper extremity. Ipsilateral Horner syndrome can be present. Partial syndromes occur frequently. Due to involvement of the cerebellar vermis, a pronounced truncal ataxia and gait impairment can be seen.

  SCA territory infarction should prompt a thorough investigation for a potential embolic source.
- *Anterior inferior cerebellar artery (AICA)*: The territory it supplies usually includes the lateral midpons, middle cerebellar peduncle, cerebellum, and the labyrinth and cochlea. The principal symptoms may include ipsilateral deafness, facial weakness, vertigo, nausea, vomiting, nystagmus, tinnitus, cerebellar ataxia, Horner syndrome, and paresis of conjugate lateral gaze. Contralateral loss of pain and temperature sensation is also seen.
- *Paramedian and short circumferential branches of the basilar artery*: Occlusion of one of short circumferential branches of the basilar artery affects the lateral two-thirds of the pons and/or middle or superior cerebellar peduncle, whereas occlusion of one of the paramedian branches of the basilar artery affects a wedge-shaped area on either side of the medial pons. Many brain stem syndromes with cranial nerve abnormalities and crossed hemiplegia have been described.
- *PCA*: Arising from the bifurcation at the top of the basilar artery, each PCA divides into two segments: (1) P1 (proximal) segment, beginning at the top of the basilar artery and extending to the posterior communicating artery takeoff, with penetrating branches to the subthalamus, thalamus, and midbrain, (2) P2 segment, beginning at the posterior communicating artery takeoff, supplies the medial inferior temporal lobe and the medial occipital lobe. Twenty percent of the time, one or both of the right or left P1 segments are atretic and the P2 segment is supplied by the ICA via the posterior communicating artery. As discussed previously, this is referred to as

a “fetal” PCA origin. The majority of ischemic syndromes result from embolism (artery-to-artery or cardiac) and less commonly atherothrombotic disease of the PCA.

- *P1 segment*: Syndromes are related to midbrain, subthalamic, and thalamic signs that vary depending on whether the embolus occludes the top of the basilar area, the right or left PCA proximal segment, or the penetrating artery branches that emerge from the proximal PCA. Top of the basilar artery occlusion results in the devastating syndrome of coma and quadriplegia, resulting from infarction of the reticular activating system and bilateral corticospinal tracts within the midbrain. Branch occlusions cause third nerve palsy and contralateral motor or sensory findings by involvement of the midbrain. The artery of Percheron is a normal anatomic variant in which a single large medial mesencephalic artery supplies both sides of the subthalamus and thalamus and part of the midbrain. Occlusion of this artery results in bilateral ptosis, paralysis of upgaze, and decreased consciousness, caused by involvement of both thalami and bilateral midbrain. When only a single penetrating artery territory is involved, small-vessel lacunar disease results (see “Lacunar or Small-Vessel Disease” later in this chapter).
- *P2 segment*: Syndromes result from involvement of cortical branches to the medial inferior temporal lobe, giving rise to memory loss and delirium, and branches to the medial occipital lobe, giving rise to contralateral homonymous visual field defects. Distal field border zone ischemia of the PCAs and MCAs gives rise to visual impairment syndromes that include inability to recognize faces or pictures or to put items in a picture together to form an object (Balint syndrome).

Small-vessel, lacunar stroke/TIA subtype A lacunar infarct results from an occlusion of a small single penetrating artery arising from the circle of Willis, the middle cerebral stem, the basilar artery, or PCA and is defined as a small noncortical lesion measuring up to 1.5 to 2 cm in diameter. The cause is lipohyalinotic narrowing or occlusion in the mid- or distal part of the artery or atherothrombotic lesion at its origin; embolism is less often the cause. Lacunar strokes account for 25% of all ischemic strokes. These strokes cause recognizable clinical syndromes that evolve over hours to days, and may be preceded by transient symptoms (lacunar TIAs). The location of the ischemia determines the nature and severity of the symptoms.

Recovery occurs often within days, but in some with especially strategically placed infarcts, significant disability is persistent and increasing age is associated with worse prognosis. Lacunar strokes are often asymptomatic but when multiple and recurrent are associated with more widespread white matter disease and an increased risk for cognitive decline and dementia.

The most common lacunar syndromes are the following:

- *Pure motor hemiparesis* is the most common lacunar stroke syndrome. It is usually from an infarct in the posterior limb of the internal capsule, corona radiata, or basis pontis. Less commonly, cerebral peduncle in the midbrain can be involved. The face, arm, leg, foot, and toes are equally paretic or plegic, but with no sensory deficit. The weakness may be intermittent (TIA), progress in a stepwise manner, or appear abruptly.
- *Pure sensory stroke* from an infarct in the ventrolateral thalamus. This type of infarct produces face, arm, and leg sensory involvement with numbness, tingling, and loss of pain and temperature. The patient generally recovers but often is left with an abnormal sensation. On rare occasions, an intolerable pain syndrome with dysesthesia occurs in the involved extremities some months afterward (Dejerine-Roussy syndrome).
    - *Sensorimotor stroke* usually results from infarction between the thalamus and internal capsule and presents with contralateral weakness of face, arm, and leg as well as decreased sensation on the same side.
- *Ataxic hemiparesis* from an infarct usually in the basis pontis or the internal capsule. This results in contralateral weakness and ataxia.
- *Dysarthria—clumsy hand syndrome* caused by lacunar infarction of the genu of the internal capsule or, less frequently, the corona radiata or the paramedian rostral pons, with resulting mild contralateral arm ataxia or arm weakness, and dysarthric speech.

Cardioembolic stroke/TIA subtype Cardiomebolic strokes account for approximately 20% of all stroke subtypes and can reach twice this number in the older population. Despite the downtrend in stroke incidence worldwide, cardioembolic stroke incidence has tripled in the last few decades and is estimated to triple again in the next 30 years, possibly due to more extensive

diagnostic evaluation. Many cardiac conditions predispose to stroke occurrence (**Table 62-1**).

TABLE 62-1 ■ EMBOLIC STROKE CLASSIFICATION

Cardiac source is definite: anticoagulant therapy generally considered standard of practice.
Left ventricular thrombi
Left atrial thrombi
Rheumatic valvular disease
Mechanical prosthetic valves
Atrial fibrillation
Nonbacterial thrombotic endocarditis
Cardiac source is definite: anticoagulation considered hazardous.
Bacterial endocarditis
Atrial myxoma
Cardiac source is possible: synonyms in the literature include "unknown source," "cryptogenic stroke"—these diagnoses are made by transthoracic or transesophageal echocardiogram.
Mitral annular calcification
Left ventricular dysfunction and dilated cardiomyopathy
Postmyocardial infarction with or without left ventricular aneurysm or thrombi
Left atrial spontaneous echo contrast
Patent foramen ovale
Atrioseptal aneurysm
Valvular strands
Ascending aortic atheromatous disease: mobile plaque 4 mm or greater
Truly unknown-source embolic stroke.

On clinical grounds, it is usually diagnosed when a sudden deficit, reaching a peak soon after its onset, appears in the territory of a large intracranial artery or in one of its major branches, and the extra- or intracranial arterial supply to this ischemic territory zone does not have a significant stenotic or thrombotic occlusive lesion. In some cases, the embolic fragment may be seen, on imaging, to occlude the vessel or a distal branch. In other cases, the suspected embolic material is not visualized because it has already been dissolved by the endogenous fibrinolytic system, but not before significant ischemia has occurred.

The clinical presentations of embolism in the anterior and posterior cerebral circulation are similar to that of artery-to-artery embolism. The nature and severity of the symptoms depend entirely on the location of the embolic fragment occluding the artery and the spared collateral circulation to its cerebral territory. Which intracranial artery or arteries that get occluded will depend on the size of the embolic fragment and the extracranial artery it enters.

The radiological characteristics of an embolic infarction differ according to the size of the embolic material as well as the diameter of the artery affected. When a more proximal large artery is involved (such as the distal ICA or proximal MCA) a large area of ischemia, involving both deep and cortical structures, occurs. When the embolic material is smaller, it lodges in more distal branches and gives rise to the more typical embolic pattern of a cortically based, wedge-shaped ischemic lesion. The clinical suspicion together with the radiological appearance of a distal cortical-subcortical lesion should prompt a more aggressive investigation for a cardioembolic source such as a structural heart or aortic lesion or an atrial arrhythmia, even if clinically occult.

Many different heart conditions predispose to cardioembolic strokes (see **Table 62-1**), but AF is not only the most prevalent of these conditions but also the one with the best evidence-based treatment strategies. Estimated to affect more than 30 million people worldwide, it is associated with a three- to fivefold risk of stroke. Particularly relevant is its occurrence in the older population where, for individuals older than 65 years, its prevalence increases by 5% per year. Not only is it more prevalent with aging but the risk of stroke associated with it also increases in older adults, a notion emphasized by the fact that the proportion of ischemic strokes attributable to AF increases with age and can be as high as 40% in the oldest old age

groups. The statistics of AF prevalence and stroke risk in the geriatric population should stress the importance of exhaustive search for AF in this age group, sometimes utilizing long-term rhythm monitoring strategies such as prolonged Holter monitoring or implantable rhythm monitoring device. In practical terms, the absence of an obvious etiology for an ischemic stroke, such as a lacunar or large vessel pattern, demands prolonged rhythm monitoring in the older population. With more studies demonstrating the effectiveness of prolonged rhythm monitoring strategies in detecting AF in stroke patients, it is also reasonable to consider such monitoring strategies in the older population, even when an alternative etiology is more immediately apparent.

Other conditions, even though less prevalent than AF, can represent high-risk conditions for embolic strokes and include congestive heart failure, recent myocardial infarction (MI) (both associated with left ventricular [LV] thrombus formation), complex aortic arch atheromas, valvular heart disease, and infective endocarditis.

Patent Foramen Ovale and Embolic Stroke Patent foramen ovale (PFO) is the consequence of failure of complete closure of the atrial septum primum and septum secundum immediately following birth, thereby leaving a communication between the right atrium and left atrium. PFO has been associated with stroke in epidemiologic studies, which indicate it is present in as many as 50% of patients with cryptogenic embolic stroke. Stroke may be more common in those with PFO because the atrial communication provides a channel by which a venous embolism can pass from the right to left side of the heart with the potential for subsequent cerebral embolism (so-called “paradoxical embolism”). Alternately, the PFO may itself be the source of thrombus formation with subsequent embolism. The PFO may be identified by transthoracic echocardiography with injection of agitated saline. Transesophageal echocardiography offers increased sensitivity. TCD ultrasound can also be used to detect the presence of right-to-left shunting by documenting the passage of agitated microbubbles into the cerebral circulation following a peripheral venous injection. It has equal or greater sensitivity than transthoracic echocardiography and can be used to guide the cardiac evaluation.

There is considerable controversy regarding the significance and therapeutic implications of PFO in stroke. PFOs are common and present in approximately 15% to 35% of the general population. After a thorough

diagnostic work-up for stroke etiology, it is often difficult to determine if a PFO is related to the stroke or an "innocent bystander." If a PFO is identified, the patient should be screened for the presence of deep venous thrombosis (DVT), which would itself be an indication for a period of anticoagulation. PFO is likely more relevant in younger patients with few or no risk factors for stroke than in the older population, where other traditional cardiovascular risk factors make other stroke etiologies more likely.

Cryptogenic stroke In up to 30% of stroke patients, despite an extensive work-up, a causative etiology cannot be found, and the stroke is classified as cryptogenic. A minimally complete etiological work-up should include neuroimaging with CT or MRI, cervical and intracranial vessel imaging, and 24-hour heart rhythm monitoring. The absence of a clear etiology is more frequently seen in younger patients but can be seen in older individuals, even when multiple cardiovascular risk factors are present. Since a large-vessel stenotic atherosclerotic lesion and a lacunar pattern must be excluded, the majority of cryptogenic strokes will fall under the category of embolic stroke of undetermined source (ESUS). This most recent stroke subclassification acknowledges that many times cryptogenic strokes will appear indistinguishable from strokes from a known embolic source. Its radiological and clinical characteristics will be of an embolic looking stroke (above) with no obvious cardiac source of embolism. This entity is important not only because it is relatively frequent but because an even more extensive work-up in this group of patients often reveals an underlying cardioembolic source, namely atrial fibrillation. Studies have shown that in this group, after more prolonged heart rhythm monitoring (at least 6 months) with implantable monitoring devices, the prevalence of paroxysmal AF can be as high as 30%. Such results have obvious clinical significance given the superior protection that long-term oral anticoagulation offers for secondary prevention, when compared to antiplatelet therapy.

For the ESUS patients with no AF detected after months of continuous rhythm monitoring, the possibility that long-term anticoagulation might be more effective than antiplatelet therapy is being investigated by current studies where structural and electrical abnormalities of the left atrium (atrial cardiomyopathy) are considered as potential markers of increased embolic risk. Like AF, such a condition is more prevalent in older adults and likely predisposes to strokes. Results from such studies will help determine the best secondary prevention strategies for this group.

Other causes of cerebral infarction Although other causes of cerebral infarction account for only 5% of all ischemic strokes, they are extremely important because their precise pathophysiologic diagnosis can lead to effective treatment.

Dissection of the cervical cerebral arteries is the most common cause of stroke in this category subtype. A dissection is a tear in the arterial wall leading to intramural hematoma formation. A subintimal dissection occurs when an intramural hematoma is between the intima and the media layers and may lead to arterial narrowing and thrombus formation. A subadventitial dissection occurs when an intramural hematoma is between the media and the adventitia layers, and may lead to the formation of a dissecting aneurysm (sometimes referred to as pseudoaneurysm).

ICA dissections usually occur 2 cm distal to the carotid bifurcation near the base of the skull. VA dissections occur in the cervical transverse foramen but more commonly at the base of the skull, at the V3-V4 segments. Intracranial dissections are less common than cervical dissections and can lead to ischemic stroke and bleeding in the subarachnoid space. Trauma, either severe or trivial, are common causes of dissection, but Valsalva maneuvers associated with coughing and vomiting, weightlifting, contact sports, or chiropractic manipulations are other recognized associations. Spontaneous dissections, without a clear antecedent cause, are not uncommon. Dissections occur at all ages but tend to be less frequent in older individuals.

The most common symptom of arterial dissection is headache or neck pain. The clinical hallmark of carotid dissection is an ipsilateral Horner syndrome usually with unilateral cervical pain. Artery-to-artery embolism or low-flow syndromes occur, just as they do for atherothrombotic disease of the ICA. Similar pathophysiologic circumstances exist for VA dissections; with them, cervical spine pain and occipital headache are the suggestive symptoms. The most common site of infarction in vertebral dissection is the lateral medulla, with or without concomitant involvement of the PICA territory in the cerebellum. Dizziness, ataxia of gait, hiccups, nausea and vomiting with a unilateral Horner syndrome, and ipsilateral face numbness with contralateral body numbness are the hallmark symptoms (Wallenberg syndrome). Occasionally, diplopia and a hoarse voice are evident. Artery-to-artery emboli arising from a thrombus at the site of dissection in the VA may migrate to distal branches of the basilar artery, producing brain stem,

cerebellar, or thalamic infarction. Sometimes spontaneous dissection can be seen in the context of underlying *fibromuscular dysplasia* (FMD), a noninflammatory, nonatherosclerotic vascular disease that can result in arterial stenosis, occlusion, aneurysm, or dissection. FMD most frequently involves the renal artery but can also involve the extracranial carotid and VA. It is usually seen in younger patients.

Vasculitis is inflammation of the blood vessels. There are numerous causes such as infection, malignancy, immune diseases, and drugs. Infectious vasculitis from bacterial or syphilitic infections is no longer a common cause of cerebral thrombosis. Infectious arteritis may rarely follow infection with varicella zoster virus (VZV), particularly if the ophthalmic division is involved, and is usually associated with involvement of larger caliber vessels. Cerebral arteritis may rarely accompany certain systemic vasculitides, including polyarteritis nodosa or Wegener granulomatosis. Necrotizing granulomatous arteritis, or primary angiitis of the central nervous system, involves the distal small branches (< 2 mm diameter) of the main intracranial arteries and produces small ischemic infarcts in the brain, optic nerve, and spinal cord. By definition, there is no systemic involvement. This rare disease is often relentlessly progressive. Presenting symptoms are varied and nonspecific, but headache is the most frequent complaint. MRI is frequently abnormal, but the findings are nonspecific. Findings include cortical and subcortical infarcts, parenchymal and leptomeningeal enhancement, subarachnoid and intraparenchymal hemorrhage, or mass lesions. Angiography can demonstrate areas of stenosis alternating with normal or dilated segments but both sensitivity and specificity are not ideal. Diagnosis of primary angiitis of the central nervous system can be difficult and typically requires either angiographic criteria be met or a tissue diagnosis.

Giant cell arteritis is a relatively common affliction of older persons, in which the external carotid system—particularly the temporal arteries—is the site of a subacute granulomatous infiltration with an exudate of lymphocytes, monocytes, neutrophilic leukocytes, and giant cells. The etiology of giant cell arteritis is not entirely clear, but it is likely secondary to multiple genetic and environmental factors with numerous infectious etiologies having been suspected in the past, including VZV. The pathogenesis is believed to involve an initial antigen-driven event that leads to the recruitment of T cells with

subsequent inflammation potentially causing vascular damage and intimal hyperplasia, the result of which can cause stenosis or occlusion.

Clinically, the chief complaint is headache or jaw claudication. Systemic manifestations, through the release of inflammatory cytokines, can include fever, loss of weight, malaise, and polymyalgia rheumatica. Blindness of one or both eyes results from occlusion of the branches of the ophthalmic artery. Occasionally, an ophthalmoplegia caused by involvement of extrinsic ocular muscles occurs. In some cases, an arteritis of the aorta and its major branches, including the carotids, subclavian, coronary, and femoral arteries, has been found at postmortem examination. Significant inflammatory involvement of the intracranial arteries is rare, but strokes occur occasionally due to occlusion of the internal carotid, middle cerebral, or vertebral-basilar system with a predilection for affecting the latter.

Per the American College of Rheumatology, the diagnosis is made if three of the five following criteria are met: (1) age of onset is greater than 50, (2) new headache, (3) temporal artery abnormality (tenderness to palpation or decreased pulsation unrelated to arteriosclerosis of the cervical arteries), (4) elevated erythrocyte sedimentation rate (ESR) ($\geq$ 50 mm/h), and (5) abnormal findings on temporal artery biopsy. The hallmark neurologic symptom is transient monocular blindness, but ischemic stroke can rarely be the presenting feature. In older patients with new-onset headaches, especially if associated with visual complaints and/or ischemic stroke, high clinical suspicion warrants obtaining urgent ESR and C-reactive protein (CRP) levels.

Moyamoya disease is a poorly understood nonatherosclerotic occlusive disorder involving the progressive stenosis of large intracranial arteries, especially the distal ICA, the stem of the MCA, and the ACA. Even though being a disease predominantly seen in children and young adults, it can rarely be seen in adults older than 60 years.

Reversible cerebral vasoconstriction syndrome (RCVS) is a reversible angiopathy that presents with severe "thunderclap" headache, often recurrent, and fluctuating neurologic symptoms and signs as well as angiographic findings of alternating areas of constriction and dilation. It affects predominantly women in the fourth and fifth decades but has been reported in patients in their sixties and seventies. Brain imaging can be normal or show cerebral infarction, hemorrhage, or transient cerebral edema. The etiology is unknown. Eclampsia, the postpartum period, head injury, migraine, and

sympathomimetic and SSRIs have all been associated with this entity. Conventional angiography is the gold standard for establishing the diagnosis although newer imaging techniques such as CTA and MRA are proving useful. Cerebrospinal fluid (CSF) is normal in most cases and this is one of the characteristics that helps distinguish this entity from primary angiitis of the central nervous system. The disease is self-limited, and, with adequate supportive care and withdrawal of the offending agent, partial or complete recovery occurs in most cases. The headaches and arterial vasoconstriction usually resolve within a few weeks.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a rare primary arteriolopathy affecting small penetrating vessels to the basal ganglia, thalamus, and cerebral white matter. The disease is caused by a variety of mutations in the *Notch3* gene. The clinical presentation is varied, but there are five primary symptoms including late-onset migraine headaches with aura, subcortical ischemic strokes, mood disturbances, cognitive impairment, and apathy. It is part of the differential diagnosis of progressive cognitive impairment and diffuse matter after disease but is rarely seen in older adults.

Binswanger subcortical leukoencephalopathy, a rare cause of dementia, is a syndrome seen with advanced small-vessel hypertensive disease. Diffuse vascular lesions are seen in the subcortical layers of the cerebral hemispheres and there is widespread white matter demyelination. It usually affects individuals around 50 years and is characterized by fluctuations in mood and consciousness and perhaps even seizures. Dementia may be an early and prominent symptom preceded or accompanied by symptoms and signs of one or more small-vessel infarctions. Confusional states, memory difficulties, and abulia are prominent, and are sometimes accompanied by focal cortical-subcortical deficits such as aphasia, apraxia, or neglect. Focal neurologic deficits or uni- or bilateral limb signs may lead to a pseudobulbar state and gait difficulties are prominent. There is often evidence of vascular compromise in other body districts. Binswanger disease must be differentiated from disorders with prominent subcortical white matter involvement on CT or MRI such as hypertensive encephalopathy, cerebral amyloid angiopathy (CAA), and CADASIL.

Hematologic diseases such as acute and chronic leukemia, essential and secondary thrombocytosis, thrombocytopenia, and sickle cell disease can be complicated by ischemic or hemorrhagic stroke. Acquired hypercoagulable

states, mainly with the detection of antiphospholipid antibodies can be part of the investigation of cryptogenic stroke in older patients while other hereditary conditions are more relevant in the investigation of stroke in the young. Cancer also increases the risk of hypercoagulability and hence ischemic stroke, and should be considered in older patients, especially when traditional stroke risk factors are absent.

Stroke can also occur during the course of a severe attack of migraine, especially migraine with aura ("migraine-induced stroke"). It is less often seen in the older population and is usually a diagnosis of exclusion, since other more common etiologies in that age group have to be considered and ruled out first.

EVALUATION

History, Physical Examination, and Initial Imaging Evaluation

The initial history and physical examination are the hallmark of the evaluation to obtain the pathophysiologic stroke or TIA subtype diagnosis. Urgent brain and vascular imaging must be performed in all patients. Noncontrast head CT, for most centers, is the initial imaging evaluation as it allows rapid exclusion of hemorrhage. While not sensitive enough to detect acute ischemic changes, especially small areas of infarction, in the first 12 hours after stroke, a head CT scan can answer the main questions in the acute setting such as:

1. Is there hemorrhage?
2. Is there an alternative diagnosis evident on initial imaging (tumor, abscess)?
3. Is the stroke already evident on initial imaging, and if so, how extensive is it?

Regarding the last question, part of the evaluation of the stroke characteristics on initial CT include estimating the extent of ischemic involvement mostly by determining areas of hypoattenuation and loss of gray-white matter differentiation. The ASPECTS scale (Alberta Stroke Program Early CT Score) is used to estimate extent of early ischemic changes and has been strongly related with prognosis. It divides the MCA-distribution territory in 10 different areas and subtracts 1 point for each area affected. A score < 6 is generally associated with a worse prognosis and is often used as

a cutoff for guiding acute interventional therapies. However, it is not a strict rule and individual case-by-case decisions are still warranted when considering acute revascularization strategies in daily practice. Besides analysis of parenchymal involvement on noncontrast CT, acute vessel imaging with CT angiogram of the head and neck should be part of the acute stroke evaluation. Knowing the anatomy of intra- and extracranial vessels as well as presence and location of a LVO is critical information in the acute decision-making process. CT Perfusion (CTP) is also part of the same radiological armamentarium, and many times provides key information on tissue viability, especially in patients who present in an extended time window from stroke onset and might still be candidates for acute intervention (MT). Details of this modality can be found elsewhere but it consists of a CT scan modality in which a contrast bolus is tracked, by serial scanning, as it passes through the tissue and the results deconvoluted into a map of perfusion times. In practical terms, the critical information one looks for when obtaining a CTP in an acute stroke is whether there is still viable tissue (ischemic penumbra) that can potentially be saved by recanalization strategies (see below). For the reasons above, the information provided by CT or CTA (and in some cases CTP) is usually fast and reliable and in most cases will suffice to help determine eligibility for acute treatment, either intravenous thrombolysis (IVT) or MT (see below).

Despite a greater accuracy for detecting acute ischemic stroke changes, MRI of the head is less practical in the hyperacute setting and is usually reserved for completion of stroke evaluation at a later time or when a challenging case demands more information for the acute decision-making process. In patients who are not candidates for acute intervention, a more complete diagnostic work-up should be initiated. MRI of the brain with diffusion-weighted imaging (DWI) is the best way of identifying cerebral infarcts acutely and accurately. Susceptibility sequences identify subacute hemorrhagic infarcts and small areas of chronic hemorrhage (microbleeds) that might be associated with small-vessel diseases such as amyloid angiopathy or hypertensive vasculopathy. MRI is far more sensitive than CT scan not only for detecting infarction at different stages but also for identifying other pathologies that can mimic an acute stroke clinically such as brain tumor, abscess, and demyelinating/inflammatory lesions. MRI also has a high sensitivity and specificity for the detection of hemorrhage.

Determining the location and pattern of ischemia on MRI is the first step in determining the most likely stroke etiology.

Imaging of the cervical and cerebral large arterial system with CTA, MRA, or carotid duplex and TCD ultrasound are modalities used for determining the vessel anatomy and its associated pathology. If done in the acute setting, CTA of the head and neck is usually sufficient and other modalities can be reserved for inconclusive studies or when administration of intravenous iodinated contrast is to be avoided. MRA of the head and neck does not offer the same anatomical resolution of the arterial system as conventional transfemoral angiography or CT angiography. MR perfusion-weighted imaging can, in an analogous way to CT perfusion imaging, identify areas of perfusion delay that indicate tissue at risk of progression to infarction.

Neurosonology tests include carotid duplex ultrasound and TCD assessment of the extra- and intracranial arterial system, respectively. Carotid duplex Doppler assesses flow in the CCA, its bifurcation, and the internal and external carotid arteries. In addition, flow in the middle portion of the VA is typically assessed to identify more proximal or distal obstructive lesions. TCD allows assessment of flow in the intracranial carotid artery and the ophthalmic artery through the transorbital approach. The transtemporal approach permits assessment of flow in the middle, anterior, and PCA stems. The occipital foramen magnum approach allows determination of flow in the distal VA and in the proximal and mid sections of the basilar artery. These tests have the advantage of being simple, noninvasive, and portable. Neurosonology tests can be used to follow the progression of the arterial pathology subacutely and chronically. Detection of microbubbles after injection of agitated saline is also helpful in detecting evidence of right to left shunt as seen in the presence of PFO. Prolonged monitoring with emboli detection and study of cerebral vasoreactivity are examples of the clinical utility of TCD in the etiological evaluation of ischemic strokes. The quantification of carotid artery atheromatous disease and its progression is an especially important use of carotid duplex combined with TCD.

Laboratory Evaluation

After completion of all acute neuroimaging modalities, the initial blood work should include the standard complete blood count, basic coagulation studies, and general chemistry examination. Checking a fasting lipid panel and

screening for diabetes with hemoglobin A_{1c} should also be performed for stroke risk factor modification. Special clotting studies are not essential, but are often useful when a hypercoagulable state is suspected, mostly in younger patients. In the majority of older patients an extensive hypercoagulable panel is usually not warranted. The screen of thyroid function with a thyroid-stimulating hormone has helped us in identifying clinically inapparent hyperthyroidism, a condition that may be associated with AF or hyperlipidemia. ESR should be considered in the older population, especially when other risk factors are missing and there is suspicion of GCA or endocarditis as the cause of the stroke.

Cardiac evaluation In addition to obtaining a baseline electrocardiogram, cardiac echocardiography and cardiac rhythm monitoring should be performed, especially when a cardiac embolism is considered in the differential diagnosis. In practical terms, unless there is an obvious causative etiology identified (lacunar or large artery atherosclerosis), given the high prevalence of AF in the older population, cardiac rhythm monitoring should always be considered in this patient population. Outpatient prolonged cardiac rhythm monitoring, ideally with an implantable loop recorder device, is very helpful if AF or other cardiogenic arrhythmias are considered and is now standard of care to look for AF in cases of suspected cardiac embolism. The suggested duration of monitoring is usually for 6 months at least, or until paroxysmal AF is identified.

Therapeutic Strategies for Acute Ischemic Stroke

With the acute onset of neurologic deficits secondary to cerebral ischemia, the goal is to facilitate or reestablish blood flow to the ischemic zone. The therapeutic strategy should always be guided by the ischemic stroke pathophysiology and mechanism, whether presumed (history and physical examination) or confirmed (history, physical examination, and diagnostic data including neuroimaging, echocardiography, heart rhythm monitoring, and laboratory testing). The diagnosis should include not only the ischemic stroke or TIA subtypes noted earlier, but also the presence or absence of pathology in the parent vessel supplying the ischemic zone and the extent of the spared collateral flow to it. The time of onset to treatment determines the therapeutic options available, which typically include (1) acute reperfusion therapies, (2) early stroke prevention strategies, and (3) long-term stroke prevention strategies.

After the pathophysiologic diagnosis has been determined and the patient has been evaluated for therapies designed to facilitate or reestablish cerebral perfusion and prevent subsequent strokes, further management efforts are directed at preventing common complications, such as DVT and aspiration pneumonia, and assisting with neurologic recovery through rehabilitation.

Acute reperfusion therapies Within the first few hours of cerebral ischemia, rapid restoration of blood flow to the affected area is the cornerstone of acute stroke treatment, and this goal is achieved by either pharmacological treatment with IVT or mechanical clot removal via endovascular thrombectomy (EVT) or MT (see **Figure 62-3**).

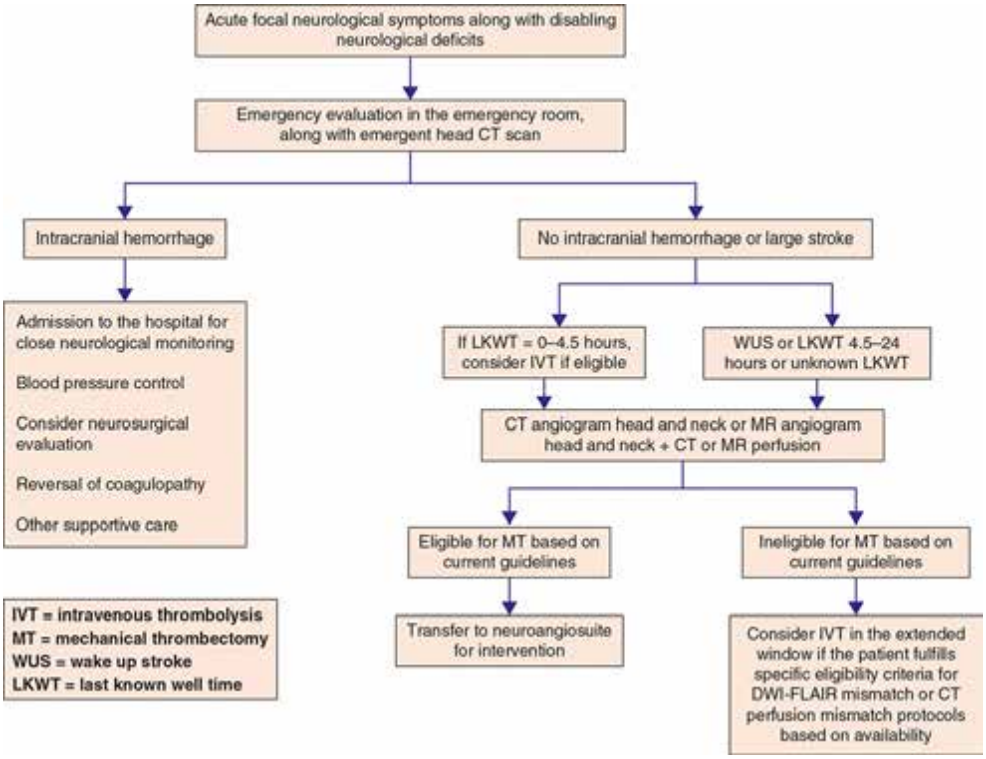

FIGURE 62-3. Algorithm for acute stroke treatment strategies.

Intravenous Thrombolysis For patients in whom treatment can be initiated within 3 hours of symptom onset, IVT with alteplase, at a dose of 0.9 mg/kg with 10% given as an immediate bolus and the remainder infused over 1 hour, has been shown to reduce stroke-related disability. In the pivotal National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke trial, patients treated with IVT had a 12% greater absolute chance of a good outcome,

defined as minimal or no stroke-related disability. This benefit was present despite a 6% risk of symptomatic intracranial hemorrhage (sICH) in the IVT group, of which more than half were fatal. Posthoc analysis of the trial did not show statistical evidence that the treatment effect varied by presumed stroke subtype, although the power to detect differences was modest. Subsequently, a trial of IVT given to patients with acute ischemic stroke within 3 to 4.5 hours showed a significant benefit of IVT as compared to placebo. In this study, the European Cooperative Acute Stroke Study (ECASS) III, the mean time to administration of rt-PA was 3 hours 59 minutes. Patients receiving IVT had a 7.2% absolute chance of a better outcome, defined as a modified Rankin score of 0 or 1 at 90 days. Mortality did not differ between the two groups. The rate of any intracranial hemorrhage was, as expected, higher in the IVT group (27% vs 17.6%) as was the rate of sICH (2.4% vs 0.3%), though lower than in the NINDS rt-PA trial. It is important to note that in ECASS III patients were excluded if older than age 80, if they had a severe stroke, or if they had a history of previous stroke and diabetes mellitus. However, updated AHA/ASA guidelines for acute stroke treatment cite a careful assessment of the published evidence to indicate that these exclusion criteria may not always be justified in clinical practice and recommend a detailed evaluation of individual risks versus benefits of IVT among patients presenting in the 3- to 4.5-hour time window. Further, both in NINDS and in ECASS III, the earlier the patients received IVT, the better were their outcomes. Therefore, it is of utmost importance to initiate thrombolytic therapy in patients with acute ischemic stroke as soon as possible, that is, aiming for shorter “door-to-needle” times.

Extended-window IVT: About 20% strokes occur during sleep, but a witnessed last-known-well (LKW) time of > 4.5 hours in these patients would disqualify them from receiving IVT due to the uncertainty regarding the true onset of stroke symptoms. Several studies have shown that a significant proportion of these patients suffer stroke symptoms in the early morning hours just before waking up because of the circadian fluctuations in blood pressure, heart rate, hemostatic processes, and occurrence of AF. Various neuroimaging modalities such as MRI (DWI-FLAIR Mismatch), CT perfusion, and MRI perfusion studies have been recently shown to reliably identify patients who may benefit from acute reperfusion therapies. The concept of DWI-FLAIR mismatch, that is, presence of an acute ischemic lesion on DWI in the absence of a hyperintense lesion on FLAIR serving as a

surrogate marker of time elapsed since the actual onset of stroke symptoms has been recently evaluated in a randomized trial of MRI-guided intravenous thrombolysis in stroke patients with unknown time of symptom onset (WAKE-UP). The basis of this clinical trial was a proposition supported by previous studies that DWI-FLAIR mismatch on an MRI was reliably able to identify a majority of the patients whose stroke symptoms started within the preceding 4.5 hours. The trial included patients who presented with a new stroke, were LKW more than 4.5 hours earlier, had no thrombectomy planned, fulfilled the prespecified imaging criteria (DWI-FLAIR mismatch), and in whom treatment with IV alteplase could be initiated within 4.5 hours of symptom recognition. The trial was terminated prematurely owing to cessation of funding after the enrolment of 503 out of 800 patients and showed an excellent outcome in 53.3% patients receiving MRI-guided thrombolysis versus 41.8% in the control arm ($p = 0.02$). Alteplase was associated with a nonsignificantly higher risk of sICH (2% vs 0.4%, $p = 0.15$) and a nonsignificantly higher mortality at 90 days (4.1% vs 1.2%). Of note, the majority of the patients treated had mild to moderately disabling stroke with a median NIHSS of 6.

In acute ischemic stroke, there is a core of irreversibly damaged tissue surrounded by an ischemic penumbra representing potentially salvageable tissue, provided normal blood circulation within that tissue is rapidly restored (discussed later in this section). Studies have shown that a CT-perfusion or an MRI-perfusion study is able to identify the core and penumbra to a reliable extent, often represented as core/perfusion mismatch. The Thrombolysis Guided by Perfusion Imaging up to 9 Hours after Onset of Stroke (EXTEND) trial compared alteplase with placebo in patients presenting between 4.5 and 9 hours after stroke onset, or after awakening with stroke (if within 9 hours from the midpoint of sleep), using predetermined CT or MRI core/perfusion mismatch criteria to select patients. After 225 of a planned 310 patients had been enrolled, the study was terminated because of a loss of equipoise after the publication of the WAKE-UP trial. This trial showed that alteplase was associated with an excellent 90-day outcome in 35.4% patients as compared to 29.5% patients receiving placebo (adjusted odds ratio 1.44, 95% CI 1.01–2.06, $p = 0.04$). The risk of sICH was higher in the alteplase group, 6.2% versus 0.9% (adjusted risk ratio 7.22, 95% CI 0.97–53.53, $p = 0.053$). The 90-day mortality was similar between the alteplase (11.7%) and placebo (8.9%)

groups (adjusted risk ratio 1.17; 95% CI 0.57–2.40; $p = 0.67$). The publication of these trials among other studies has contributed to the expansion of IVT eligibility in a subset of acute stroke patients in whom the time they were LKW was either unknown or more than 4.5 hours prior to waking up with stroke symptoms, depending upon the center they are treated at and the resources available at that center. One limitation of the MRI-based approach is that it requires immediate access to an MRI scanner and collateral information from the patient/family members to establish MRI safety (absence of ICD/pacemakers or metallic prosthesis in the patient's body). On the other hand, a CT-perfusion-based approach requires access to an automated software that enables rapid calculation of ischemic core and penumbra estimates. Moreover, in both these trials, there were a substantial proportion of patients with a LVO who may have qualified for MT based on the updates from two novel endovascular trials that were subsequently published (discussed later in this section). These limitations have restricted the widespread adoption of these approaches depending upon the region, access to care, and resources available, but they may remain reasonable options for a select subgroup of acute stroke patients. The 2019 updates for the early management of acute ischemic stroke published by the AHA/ASA suggest the MRI-based approach (DWI-FLAIR mismatch) for IVT as a reasonable choice for a carefully selected group of acute ischemic stroke patients in the extended time window.

Because of the risks of hemorrhage, the decision to administer IVT should be based on an individual assessment of the benefits and risks for the specific individual, with careful attention to the treatment inclusion and exclusion criteria. Patients with acute disabling neurological deficits without hemorrhage or established infarct on initial head CT should be considered for IVT. Exclusion criteria must be reviewed carefully prior to IV rt-PA administration. An important concept to understand is the disabling nature of the neurological symptoms at presentation. A phase IIIb, double-blind, multicenter study to evaluate the efficacy and safety of alteplase in patients with mild stroke, rapidly improving symptoms, and minor neurologic deficits (the PRISMS trial) tested the efficacy of IV alteplase versus aspirin for emergent stroke with presenting symptoms that were deemed to be nondisabling in nature by the treating physician. Of a planned 948 patients, the trial was able to recruit 313 patients and failed to show a benefit of IV alteplase over aspirin, and consequently the current AHA/ASA guidelines

recommend against IVT administration among patients who do not have presenting neurological deficits that would interfere with their daily lives. There has been concern about treatment of older adults because age may be a risk factor for IVT-related hemorrhage; however, the NINDS trial data show that this increased risk does not outweigh the potential benefit in older persons.

Although the rate of sICH after IVT is relatively low, it remains the most feared and sometimes fatal complication of this treatment. Rapid identification and administration of procoagulant factors such as cryoprecipitate or prothrombin complex concentrates (PCC) or tranexamic acid (or a combination of these aforementioned options) along with the provision of neurosurgical and hematological consultations under the care of experienced neurocritical care teams form the mainstay of management of sICH after IVT administration.

More recently, tenecteplase (TNK) instead of alteplase as the thrombolytic agent in acute ischemic stroke has been gaining some traction among the vascular neurology community. TNK is a recombinant tissue plasminogen activator like alteplase but exhibits a higher degree of fibrin specificity and a longer half-life that allows for a single bolus dose administration. Preliminary studies have shown that it is at least comparable, and in some situations, could be more effective than alteplase for acute ischemic stroke. Consequently, many centers worldwide are beginning to offer TNK as an alternative to alteplase as more evidence is awaited.

Mechanical thrombectomy EVT with thrombolytics/thrombus retrieval devices had been studied over the past two decades over many studies without much success in clinical outcomes. But, in 2015, several pivotal randomized clinical trials established an overwhelming benefit of EVT/MT in treatment of patients with acute ischemic stroke and a LVO who fulfilled certain criteria, establishing this treatment as a standard-of-care for this patient population. The reasons for such tremendous success of the newer trials were thought to be related to their better patient selection criteria and utilization of more effective reperfusion devices. The exact details differ among these trials, but overall, there were many common features that contributed to the success of these studies and EVT/MT, in general. First, all these trials required the presence of a LVO defined as an occlusion of the intracranial segment of the ICA or proximal segment of the middle cerebral artery (MCA), denoted by M1. The more distal blood vessels are denoted by

M2, M3, and so on. Very few patients harbored an occlusion of M2 in these trials and none had more distal occlusions. Second, all trials except MR CLEAN (Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands) required evidence of absence of severe ischemic changes in the affected brain tissue on a noncontrast CT scan represented by an Alberta Stroke Program Early CT Score (ASPECTS), and although MR CLEAN did not have these requirements in the study entry criteria, it recruited very few patients who had evidence of advanced ischemic changes. Third, all trials encouraged rapid attempt at recanalization, and while most of the trials implemented 0- to 6-hour time window since LKW for study entry, ESCAPE (endovascular treatment for small core and anterior circulation proximal occlusion with emphasis on minimizing CT to recanalization times) and REVASCAT (randomized trial of revascularization with Solitaire FR device versus best medical therapy in the treatment of acute stroke due to anterior circulation LVO presenting within 8 hours of symptom onset) proved the benefit of MT in patients up to 8 hours from symptom onset. Fourth, for the majority of the patients, MT was carried out using the second-generation stent retriever devices. In this procedure, a catheter is advanced into an artery, and using fluoroscopic guidance, a stent retriever is inserted into the catheter. The stent reaches past the clot, expands to stretch the walls of the artery, and is retrieved, removing the clot. Finally, these trials required the patients to have decent baseline level of functioning for them to be able to participate. This allowed for adequate participation in the rehabilitation therapies following the thrombectomy procedure and promoted neurological recovery among the treated patients. A meta-analysis combining data from 1287 patients from five of these pivotal trials showed that the rate of successful recanalization among patients undergoing MT was 71%. Patients who underwent MT had a higher likelihood of achieving good 90-day clinical outcome with return to functional independence, 46% versus only 26.5% in the control group. Finally, the number needed to treat for one patient to have reduced disability was found to be 2.6, thus confirming the highly effective nature of MT as a treatment for anterior circulation LVO among acute ischemic stroke patients with disabling symptoms and who were LKW within 8 hours. Moreover, this benefit persisted across all age groups, even octogenarians, and although the overall mortality remained lower in the intervention group (15.3% versus 18.9% in the control group), this difference was not shown to be statistically significant.

The penumbra concept for patient selection: An intracranial occlusion causing complete cessation of blood flow to brain tissue it supplies renders that tissue at risk of irreversible damage. The larger the area supplied by this occluded vessel, the larger the tissue is at risk and while intracranial and extracranial collateral circulation may help compensate for some of the lack of blood flow, as time passes, even the collateral circulation runs the risk of failing, thereby causing irreversible tissue injury. Moreover, the normal average blood flow is about 50 mL/100 g/min. When this flow drops to 20 to 30 mL/100 g/min, there is a selective loss of neuronal functions with electrical failure and inability to conduct the electrical impulses, but the cell structure is still intact. However, when this flow reduces below a critical level between 10 and 20 mL/100 g/min, there is loss of ATP function of the cell resulting in cell membrane damage, swelling, and subsequent cell death. Because of a close interplay of these phenomena, an intracranial occlusion leads to the formation of three zones of brain injury (see **Figure 62-4**): the ischemic core (tissue irreversibly injured), the ischemic penumbra (tissue with very slow blood flow, with cessation of neuronal functions but intact cell structure allowing for slow functional recovery if adequate blood flow is rapidly restored), and the zone of benign oligemia (tissue with milder reduction in the blood flow that does not lead to tissue at risk). Over the last few years, neuroimaging techniques with CT perfusion and MRI perfusion have been developed that can rapidly provide a reliable estimate of these zones of ischemia, penumbra, and benign oligemia. Although both the modalities have their pros and cons, they have been increasingly used in acute stroke imaging and form the basis of DAWN (DWI or CTP assessment with clinical mismatch in the triage of wake-up and late presenting strokes undergoing neurointervention) and DEFUSE 3 (endovascular therapy following imaging evaluation for ischemic stroke 3) trials published in 2018, which allowed for expansion of MT in patients who presented with acute disabling stroke symptoms beyond 6 hours of LKW time and had a salvageable penumbra measured by the automated quantitative perfusion on CT perfusion or an MR perfusion study (see **Figure 62-5**). There were some differences in the clinical and imaging selection between the two trials, but essentially DAWN enrolled patients between 6 and 24 hours of their LKW time and DEFUSE 3 enrolled patients within 6 to 16 hours of their LKW time. DAWN enrolled 207 patients and showed the largest treatment effect size in terms of functional outcome with 49% of the patients undergoing MT

achieving functional independence at 3 months versus only 13% patients in the medical management arm. Similarly, in DEFUSE, enrollment was terminated early for efficacy after 182 patients were randomized and showed the rate of return to functional independence in 41% patients undergoing MT versus only 15% in the medical management arm. The findings from these trials have shifted the paradigm of stroke treatment from being a strictly time-based approach toward a more inclusive salvageable tissue-based approach and expanded its eligibility to a much broader population. Like in the early time window, the efficacy for MT has been unequivocally accepted for all adult age groups, including octogenarians. Although these trials established the benefit of MT among patients in the extended time window, it is very important to understand that the patients who fulfill these criteria are relatively few and the survivability of the brain tissue depends upon the collateral circulation status of a patient. With time, this collateral circulation may fail, although definite timepoints at which this may happen are almost impossible to predict. Thus, even when dealing with a patient with favorable core/perfusion mismatch showing salvageable penumbra, it is crucial that these patients receive MT without any additional delay to harness the maximal benefit from reperfusion.

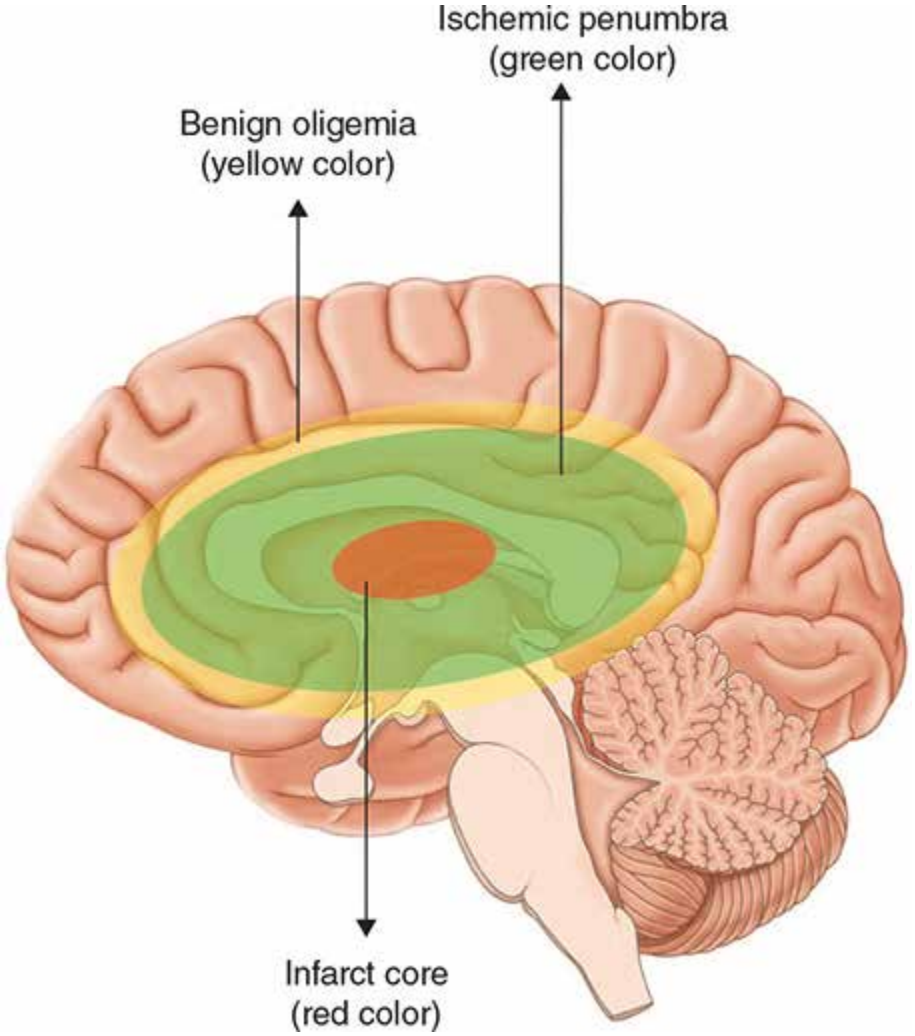

FIGURE 62-4. Diagram of a cerebral hemisphere, lateral aspect, indicating the zones of ischemia (red), penumbra (green), and benign oligemia (yellow) that form in an acute ischemic stroke due to an intracranial LVO.