on placebo. In the rTPA group, there was a significant 12% absolute increase in the number of patients with only minimal disability (32% on placebo and 44% on rtPA) and a nonsignificant 4% reduction in mortality (21% on placebo and 17% on rtPA). Thus, despite an increased incidence of symptomatic intracranial hemorrhage, treatment with IV rtPA within 3 h of the onset of ischemic stroke improved clinical outcome.

Three subsequent trials of IV rtPA did not confirm this benefit, perhaps because of the dose of rtPA used, the timing of its delivery, and small sample size. When data from all randomized IV rtPA trails were combined, however, efficacy was confirmed in the <3-h time window, and efficacy likely extended to 4.5 h and possibly to 6 h. Based on these combined results, the European Cooperative Acute Stroke Study (ECASS) III explored the safety and efficacy of rtPA in the 3- to 4.5-h time window. Unlike the NINDS study, patients older than 80 years of age and diabetic patients with a previous stroke were excluded. In this 821-patient randomized study, efficacy was again confirmed, although the treatment effect was less robust than in the 0- to 3-h time window. In the rtPA group, 52.4% of patients achieved a good outcome at 90 days, compared to 45.2% of the placebo group (odds ratio [OR] 1.34, $p = .04$). The symptomatic intracranial hemorrhage rate was 2.4% in the rtPA group and 0.2% in the placebo group ($p = .008$).

Based on these data, rtPA is approved in the 3- to 4.5-h window in Europe and Canada, but is still only approved for 0–3 h in the United States and Canada. Use of IV tPA is now considered a central component of primary stroke centers (see below). It represents the first treatment proven to improve clinical outcomes in ischemic stroke and is cost-effective and cost-saving. Advanced neuroimaging techniques (see neuroimaging section below) may help to select patients beyond the 4.5-h window who will benefit from thrombolysis, but this is currently investigational. The time of stroke onset is defined as the time the patient's symptoms were witnessed to begin or the time the patient was last seen as normal. Patients who awaken with stroke have the onset defined as when they went to bed. Table 446-1 summarizes eligibility criteria and instructions for administration of IV rtPA.

TABLE 446-1 ADMINISTRATION OF INTRAVENOUS RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR (rtPA) FOR ACUTE ISCHEMIC STROKE (AIS)[a]

Indication	Contraindication
Clinical diagnosis of stroke	Sustained BP >185/110 mmHg despite treatment
Onset of symptoms to time of drug administration ≤4.5 h[b]	Platelets <100,000; HCT <25%; glucose <50 or >400 mg/dL
CT scan showing no hemorrhage or edema of >1/3 of the MCA territory	Use of heparin within 48 h and prolonged PTT, or elevated INR
Age 18 ≥ years	Rapidly improving symptoms
Consent by patient or surrogate	Prior stroke or head injury within 3 months; prior intracranial hemorrhage
	Major surgery in preceding 14 days
	Minor stroke symptoms
	Gastrointestinal bleeding in preceding 21 days
	Recent myocardial infarction
	Coma or stupor
Administration of rtPA	
IV access with two peripheral IV lines (avoid arterial or central line placement)	
Review eligibility for rtPA	
Administer 0.9 mg/kg IV (maximum 90 mg) IV as 10% of total dose by bolus, followed by remainder of total dose over 1 h	
Frequent cuff blood pressure monitoring	
No other antithrombotic treatment for 24 h	
For decline in neurologic status or uncontrolled blood pressure, stop infusion, give cryoprecipitate, and reimage brain emergently	
Avoid urethral catheterization for ≥2 h	

[a]See Activase (tissue plasminogen activator) package insert for complete list of contraindications and dosing. [b]Depending on the country, IV rtPA may be approved for up to 4.5 h with additional restrictions.

Abbreviations: BP, blood pressure; CT, computed tomography; HCT, hematocrit; INR, international normalized ratio; MCA, middle cerebral artery; PTT, partial thromboplastin time.

ENDOVASCULAR REVASCULARIZATION

Ischemic stroke from large-vessel intracranial occlusion results in high rates of mortality and morbidity. Occlusions in such large vessels (middle cerebral artery [MCA], intracranial internal carotid artery, and the basilar artery) generally involve a large clot volume and often fail to open with IV rtPA alone. Therefore, there is growing interest in using thrombolytics via an intraarterial route to increase the concentration of drug at the clot and minimize systemic bleeding complications. The Prolyse in Acute Cerebral Thromboembolism (PROACT) II trial found benefit for intraarterial prourokinase in acute MCA occlusions up to the sixth hour following onset of stroke. Intraarterial treatment of basilar artery occlusions may also be beneficial for selected patients. Intraarterial administration of a thrombolytic agent for acute ischemic stroke (AIS) is not approved by the U.S. Food and Drug Administration (FDA); however, many stroke centers offer this treatment based on these data.

Endovascular mechanical thrombectomy has been studied as an alternative or adjunctive treatment of acute stroke in patients who are ineligible for, or have contraindications to, thrombolytics or in those who failed to achieve vascular recanalization with IV thrombolytics (see Fig. 446-15). The Mechanical Embolus Removal in Cerebral Ischemia (MERCI) and multi-MERCI single-arm trials found that an endovascular thrombectomy device restored patency of occluded intracranial vessels within 8 h of ischemic stroke symptoms compared with a historical control group. Recanalization of the target vessel occurred in 48–58% of treated patients and in 60–69% of patients after use of adjuvant endovascular methods, and successful recanalization at 90 days correlated well with favorable outcomes. Based on these nonrandomized data, the FDA approved this device as the first device for revascularization of occluded vessels in AIS even if the patient has been given rtPA and that therapy has failed. The Penumbra Pivotal Stroke trial tested another mechanical device that showed even higher rates of recanalization and led to FDA clearance of the tested device as well. More recently, two Stentriever devices (nondetachable stents) were shown to significantly improve vascular recanalization compared to the first approved MERCI device, approaching recanalization rates of 90% in most large intracranial vessels.

In 2013, three randomized endovascular trials with nonendovascular controls found no benefits to endovascular therapy. The largest was the Interventional Management of Stroke III trial that randomized 656 AIS patients within 3 h of onset to IV rtPA (0.9 mg/kg) alone versus IV rtPA (0.6 mg/kg) followed by endovascular adjuvant treatment with IA rtPA, or endovascular thrombectomy as soon as possible. Outcomes between these groups were not significantly different, and there were more complications (groin bleeding chiefly) in the endovascular group. The SYNTHESIS trial based in Italy randomized 363 patients to IV rtPA versus intraarterial rtPA for patients within 3 h of stroke onset. No differences were found between the groups at 90 days. These two relatively large trials indicate that endovascular therapy using principally intraarterial rtPA is not better than IV therapy, but many questions remain. Relatively few patients received mechanical clot retraction therapies, and those who did received what we now know were inferior devices. Trials assessing more efficacious thrombectomy devices are currently ongoing.

Because use of endovascular devices in combination with rtPA appears relatively safe, some centers continue to offer endovascular therapy. This applies to patients who are not eligible for IV rtPA (recent surgery, stroke following cardiac catheterization, etc.), and some continue to use thrombectomy because of perceived better