Advances in Treatment of Acute Ischemic Stroke

Written by Brian Hoyle

Acute ischemic stroke that results from large artery or small vessel atherosclerosis, atrial fibrillation, cervical artery dissection, and unknown etiologies is an important health concern. In the developed world, stroke is the leading cause of disability and the third-most common cause of death, according to Brian van Adel, MD, PhD, McMaster University, Hamilton, Ontario, Canada.

Clinical outcome of stroke is measured with the modified Rankin score. This scale ranks patients in terms of the degree of functional disability, with scores indicating unfavorable or favorable outcomes (ie, return to residence and resumption of some/all aspects of daily living), with higher scores indicating progressively severe degrees of mobility limitation and ultimately death (Table 1).

Ischemia-related damage to the brain depends on the occlusion size, severity of blood flow reduction, duration of ischemia, efficiency of collateral circulation, blood flow restoration, and other factors. Thrombolysis and vessel recanalization are the only neuroprotective treatments supported by clinical evidence [Jauch EC et al. *Stroke.* 2013]. Recanalization can be done pharmaceutically and mechanically. However, vessel restoration does not always result in a good outcome.

Likewise, the outcome of thrombolysis therapy through intravenously administered tissue plasminogen activator (tPA) can vary; it is especially effective when done soon after the ischemic stroke (within 3 hours). Protracted delays before tPA treatment increase the risk of symptomatic intracranial hemorrhage. tPA therapy yields good recanalization in occluded proximal vessels when applied to distal small clots in the intracranial circulation, but the outcome is not as good for other locations, including the basilar artery and internal carotid artery [Bhatia R et al. *Stroke.* 2010].

The time to treatment is crucial. Every minute that a large-vessel ischemic stroke is untreated, 2 million neurons die, and aging is accelerated by over 3 weeks [Saver JL. *Stroke.* 2006]. Current unknowns about acute ischemic stroke treatment through intravenous tPA include the rate of infarct progression, how collateral circulation influences recovery, and the influence of other factors, such as the composition of a clot.

Treatment has advanced from catheter-mediated delivery of tPA for intra-arterial fibrinolysis in the late 1990s to ultrasound coil retrievers and aspiration in the next decade and to the use of various designs of stent retrievers in the past few years.

Table 1. Modified Rankin Score

Outcome: Score	Symptom
Favorable	
0	No symptoms at all
1	No significant disability
2	Slight disability
Unfavorable	
3	Moderate disability
4	Moderately severe disability
5	Severe disability
6	Death

In particular, optimistic results have resulted through the use of newer stent retrievers in the following studies: MR CLEAN [ISRCTN10888758; Fransen PSS et al. *Trials.* 2014], ESCAPE [NCT01778335; Goyal M et al. *New Engl J Med.* 2015], EXTEND-IA [NCT01492725; Campbell BCV et al. *New Engl J Med.* 2015], SWIFT PRIME [NCT01657461; Saver JL et al. *New Engl J Med.* 2015], and REVASCAT [NCT01692379; Jovin TG et al. *New Engl J Med.* 2015]. These trials have spurred the recommended use of mechanical thrombectomy in addition to intravenous tPA to treat acute ischemic stroke with large-artery occlusions within 6 hours of symptom onset. Mechanical thrombectomy should be done as soon as possible.

Current Treatment of Superficial Vein Thrombosis and Cerebral Venous Thrombosis

Written by Emma Hitt Nichols, PhD

Recommendations for treatment of superficial vein thrombosis (SVT) of the legs now include anticoagulation; however, the low quality of evidence to support this recommendation and the uncertainty of cost-effectiveness have resulted in the question: Do patients with SVT require treatment? Hervé Décousus, MD, CHU de Saint-Etienne, Saint Etienne, France, discussed the management of spontaneous acute SVT of the legs.

Several studies have demonstrated that deep vein thrombosis (DVT) and pulmonary embolism (PE) are present in 25% to 29% of patients who present with primary or secondary SVT [Frappé P et al. *J Thromb Haemost.* 2014; Galanaud JP et al. *Thromb Haemost.* 2011; Décousus H et al. *Ann Intern Med.* 2010]. In addition, patients with isolated SVT are at an increased risk of developing a subsequent DVT or PE between 3 and 6 months, with rates of up to 3.1% and 0.9% for DVT and PE, respectively [Décousus H et al. *J Thromb Haemost.* 2015]. Patients with SVT are at risk of SVT

extension, with 3.6% of extensions occurring ≤3 cm from the saphenous-femoral junction and 3.7% occurring farther away [Leizorovicz A et al. *Blood*. 2013]. Importantly, SVT extension is associated with the development of a subsequent DVT or PE. Therefore, Prof Décousus recommends that patients who present with SVT should be evaluated for PE symptoms and an ultrasound should be conducted to determine if DVT is present.

Patients with SVT should receive anticoagulation therapy to prevent symptomatic thromboembolism. The randomized, double-blind STENOX trial [Superficial Thrombophlebitis Treated by Enoxaparin Study Group. *Arch Intern Med*. 2003] demonstrated that low molecular weight heparin (LMWH) for 12 days reduced the rate of DVT and SVT for over 80 days; however, most events occurred after LMWH was stopped. This indicates that anticoagulation is effective, but 12 days is not adequate in duration. Furthermore, the VESALIO [VESALIO Investigators Group. *J Thromb Haemost*. 2005] and STEFLUX trials [Cosmi B et al. *J Thromb Haemost*. 2012] demonstrated that 30 days of LMWH is also insufficient. By contrast, the CALISTO trial [Décousus H et al. *N Engl J Med*. 2010] demonstrated that 2.5 mg of fondaparinux for 45 days reduced the risk of death or symptomatic thromboembolism without increasing the risk of bleeding and did not cause catch-up phenomena to occur. In addition, fondaparinux for 45 days reduced the risk of PE, DVT, SVT recurrence, and SVT extension ≤3 cm from the saphenous-femoral junction (Figure 1). In the CALISTO trial, even patients with no known risk factors for thromboembolism derived benefit from fondaparinux therapy for 45 days.

Therefore, the current American College of Chest Physicians recommendations for the treatment of SVT of the legs suggest a prophylactic dose of fondaparinux or LMWH for 45 days, with 2.5 mg of fondaparinux being the preferred drug [Kearon C et al. *Chest*. 2012]. In addition, a Cochrane review found that 2.5 mg of fondaparinux for 45 days for the treatment of SVT was a valid treatment, but the authors could not reach a conclusion regarding LMWH, unfractionated heparin, or nonsteroidal anti-inflammatory drugs [Di Nisio M et al. *Cochrane Database Syst Rev*. 2013].

However, there are still unanswered questions regarding the optimal treatment of SVT. For example, the optimal dose and duration of LMWH has not yet been established, there are currently no data regarding the safety and efficacy of the new oral anticoagulants, and fondaparinux has not been tested in patients who are pregnant or in patients with cancer or a recent history of venous thromboembolism (VTE).

Another important small vein thrombosis is that of the cerebral veins and dural sinuses. Cerebral venous

Figure 1. Effect of 45 Days of Fondaparinux on Thromboembolism Risk After SVT
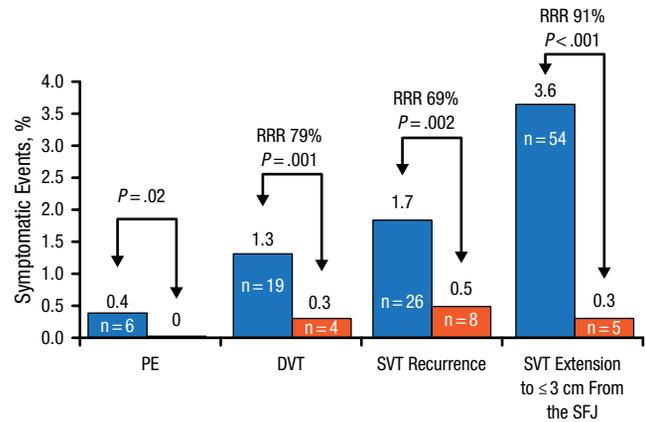
Some patients had more than one event. Death: fondaparinux, n=2 (cancer); placebo, n=1 (acute heart failure).

DVT, deep vein thrombosis; PE, pulmonary embolism; RRR, relative risk reduction; SFJ, saphenous-femoral junction; SVT, superficial vein thrombosis.

Source: Décousus H et al. *N Engl J Med*. 2010.

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thrombosis (CVT) has a much lower incidence than DVT or PE, but it occurs more frequently in children and younger adults. Jonathan M. Coutinho, MD, PhD, Academic Medical Center, Amsterdam, The Netherlands, discussed the epidemiology, clinical manifestations, and management of CVT.

CVT encompasses sinus thrombosis and cerebral venous thrombosis, which frequently occur in the same patient. Sinus thrombosis causes intracranial hypertension due to decreased cerebrospinal fluid absorption (Table 1). By contrast, cerebral venous thrombosis causes site-specific congestion leading to edema, and potentially infarction and hemorrhage.

The risk factors of CVT are partly similar to those of VTE, such as thrombophilia, cancer, and pregnancy [Lauw MN et al. *Semin Thromb Haemost*. 2013]. However, CVT-specific risk factors include neurosurgery, head trauma, lumbar puncture or epidural anesthesia, and local infections [Saposnik G et al. *Stroke*. 2011]. Diagnosis requires magnetic resonance imaging (MRI) and magnetic resonance venography (MRV), or computed tomography (CT) venography in centers without access to MRV or for patients who cannot undergo an MRI scan. MRI is superior to CT for detection of concomitant brain parenchymal lesions (Table 2).

Anticoagulation with LMWH is currently the standard treatment to reduce the risk of death or dependency. This is based on data from 2 small trials that, when taken

Table 1. Common Signs and Symptoms of Cerebral Venous Thrombosis

Symptom	Estimated Prevalence
Headache	90
Paresis	40
Seizures	40
Aphasia	20
Vision loss	10
Comatose	5

Data presented in percentages.

Source: Ferro JM et al. *Stroke.* 2004.

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Table 2. Potential Concomitant Parenchymal Lesions Due to Cerebral Venous Thrombosis

Parenchymal Lesion	Estimated Prevalence
Intracerebral hemorrhage	40-50[a]
Cerebral edema	40-50[a]
Subarachnoid hemorrhage	10-15
Subdural hemorrhage	< 5

Data presented in percentages.

[a]Edema and intracerebral hemorrhage often occur simultaneously.

together, resulted in a risk ratio of 0.46, albeit with a wide confidence interval (95% CI, 0.16 to 1.31) and lack of statistical significance ($P = .12$) [Coutinho J et al. *Cochrane Database Syst Rev.* 2011]. However, Dr Coutinho pointed out that in the heparin arm, none of the patients developed a new intracerebral hemorrhage despite many having hemorrhage at baseline, and 2 patients in the placebo arm developed probable PE. Endovascular treatment should be used only in severe cases; however, the ongoing TO-ACT trial should answer the question of when thrombolysis or thrombectomy should be used [Coutinho JM et al. *Int J Stroke.* 2013].

The standard treatment for ambulatory patients after CVT is a vitamin K antagonist. Although international guidelines recommend oral anticoagulation for 3 to 6 months in provoked cases and 6 to 12 months for unprovoked cases, the optimal duration is still not established [Saposnik G et al. *Stroke.* 2011; Einhäupl K et al. *Eur J Neurol.* 2010]. There are little data for use of nonwarfarin oral anticoagulants in CVT, although case series on this topic were recently published (PubMed ID 25070963).

With adequate treatment, the prognosis of patients with CVT is quite good, with only 15% to 20% having permanent disability and 5% to 10% experiencing death.