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Current endovascular treatment of acute stroke and future aspects

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Acute ischemic stroke remains a condition of high morbidity and mortality. Until now, the only established therapy has been intravenous (IV) tissue-type plasminogen activator (tPA). Only 3–10% of patients with acute ischemic stroke receive this treatment.On the basis of data from part 3 of the European Collaborative Acute Stroke Study (ECASS III), the time window for beneficial treatment of ischemic stroke with IV tPA has been extended from 3 to 4.5 h after the onset of stroke symptoms. Beyond that window of opportunity, and additionally to IV treatment, interventional stroke therapy has assumed an important role for the treatment of acute ischemic stroke.Currently, new promising pharmacological and mechanical treatment options are being established as routine procedures to achieve a further improved outcome for stroke patients.

Introduction

After myocardial infarction and cancer, stroke is the third most common cause of death in the western world, affecting an estimated 700,000 Americans each year, and is the most common cause of severe disability [1]. Some 30–50% of stroke survivors do not regain functional independence and 15–30% of these remain permanently disabled. Thus, stroke is a massive financial and personal burden on our society [2]. For someone who is having a stroke 'Time is Brain'. Earlier treatment is associated with better outcome. To achieve this, acute stroke protocols are initiated to identify patients within the therapeutic time window for thrombolytic and mechanical recanalization therapies.

In 1996, as a result of the National Institute of Neurological Disorder and Stroke (NINDS) and rtPA Stroke Study Group trial, the US Food and Drug Administration (FDA) approved IV thrombolysis with recombinant tissue plasminogen activator (rtPA, alteplase) for the treatment of ischemic stroke within 3 h of onset [3]. Thus, IV rtPA thrombolysis was the first approved treatment that attacks the acute vessel occlusion directly. It is now accepted as a class 1A level of evidence intervention for acute ischemic stroke [4].

Analysis of major randomized placebo-controlled IV rtPA stroke trials, as ATLANTIS I and II (Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke), ECASS I and II (European Cooperative Acute Stroke Study), and NINDS I and II showed a benefit up to 3 h from the onset of stroke symptoms and suggested a potential benefit beyond 3 h for some patients [5,6]. The ECASS-III trial confirmed a treatment window up to 4.5 h for IV rtPA therapy [7].

Despite its promise and the use of different drugs, the recanalization rates of IV rtPA for proximal arterial occlusion range from only 10% to 30% and the NINDS trial data showed a 12% increase at 3 months in better outcomes between the placebo and rtPA groups [8].

Drugs used in acute stroke therapy

Drug therapy is a relatively recent approach to the treatment of stroke, and a large amount of research is focused on finding effective new drugs that can minimize stroke damage. The most relevant drugs evaluated for acute stroke therapy are summarized in Table 1.

Plasminogen activators

Plasminogen activators are the primary drugs used as thrombolytic agents in acute stroke therapy. These drugs act by converting plasminogen into plasmin. Plasmin unlocks fibrinogen, fibrin monomers and cross-linked fibrin (as found in a thrombus) into fibrin degradation products [9].

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TABLE 1

Drugs used in endovascular therapy for acute stroke.

Group	Drug	Effect
Drugs to improve blood flow	Heparin	Antithrombotic
	Abciximab	Antiplatelet
	Ancrod	Fibrinogen depleting
Thrombolytics	Streptokinase	Plasminogen activators
	Urokinase	
	Prourokinase	
	Alteplase	
	Reteplase	
	Tenecteplase	
	Tissue plasminogen activator	
	Alfimeprase	Direct acting fibrinolytics
	BB10153	
	Desmoteplase	
New drugs under evaluation	V10153	
	Microplasmin	

Streptokinase binds to plasminogen and the streptokinase/plasminogen complex then serves as a plasminogen activator. It is a protein derived from group CS-hemolytic streptococci, which showed significant rates of ICH and systemic hemorrhage [10]; thus, it is no longer used for acute stroke therapy; rather, *Urokinase*, a serine protease with a plasma half-life of 14 min, is used [9]. The randomized trial of intra-arterial infusion of urokinase within 6 h of middle cerebral artery stroke: the middle cerebral artery embolism local fibrinolytic intervention trial (MELT), suggested that intra-arterial fibrinolysis has the potential to increase the likelihood of excellent functional outcome [11].

Prourokinase (r-prourokinase) is the proenzyme precursor of urokinase. Despite the favorable results in the PROACT (Prolyse in Acute Cerebral Thromboembolism) I and II trials [12,13], the FDA did not approve its use in IA stroke therapy.

Alteplase (recombinant human tissue-type plasminogen activator; rtPA) is a serine protease with a plasma half-life of 3.5 min. This short half-life and the limited penetration of the clot, because of strong binding with surface fibrin, delay recanalization and increase the risk of recurrent occlusion. By the administration of heparin or antiplatelet drugs, reocclusion may be reduced. Moreover, rtPA seems to have some neurotoxic properties, including activation of metalloproteinases, which may result in increased blood–brain barrier permeability leading to cerebral hemorrhage and edema, as well as amplification of calcium currents through the N-methyl-D-aspartate receptor. This leads to excitotoxicity and neuronal death [14]. Nevertheless, rtPA represents the first line therapy in the treatment of acute ischemic stroke.

More recently licensed plasminogen activators are variants of tPA. These include *Reteplase*, a truncated tPA variant with a longer half-life and *Tenecteplase*, a bioengineered tPA variant. Because of their longer half-lives, Reteplase and Tenecteplase can be given as a bolus injection, thereby simplifying administration [15]. A case study reported 84% recanalization and no ICH with IA Reteplase in combination with mechanical thrombolysis [16]. A pilot clinical trial with Tenecteplase, was terminated owing to symptomatic and asymptomatic ICHs (15% and 23%, respectively) [17].

Direct fibrinolytics

New fibrinolytic agents currently under development were built upon advances of tPA derivatives developed to produce less bleeding [18].

Alfimeprase (ARCA *biopharma*, Broomfield, CO, USA), a recombinant, truncated form of fibrolase, has been developed to accelerate lysis. It is designed to dissolve clots by directly degrading fibrin when delivered through a catheter directly into the thrombus and is inactivated locally by circulating alpha-2 macroglobulin. Because there is no need for plasmin generation, alfimeprase has the potential to degrade fibrin more rapidly than tPA. This should result in faster recanalization and lower hemorrhagic risk [19]. Nevertheless, alfimeprase failed to meet the key efficacy end points of revascularization in the phase II trial CARNEROS-1 (Proof-of-Concept Study of the Safety and Efficacy of Alfimeprase to Rapidly Open Arteries and Restore Brain Function Following a Stroke). The full results of this trial have not yet been published.

BB10153 (British Biotech, Oxford, England), a variant form of plasminogen, has the plasminogen activator cleavage site replaced with a thrombin cleavage site. Like plasminogen it binds to fibrin and gets converted to plasmin by fibrin-bound thrombin. In a phase II dose-escalation study 34% of patients achieved complete flow in the infarct-related artery. There were no intracranial bleeds [20] and based on these data, BB10153 is undergoing continued investigation.

Desmoteplase (Paion, Aachen, Germany), a recombinant analog of the full-length plasminogen activator isolated from the saliva of the vampire bat, demonstrated safety in the Desmoteplase in Acute Ischemic Stroke (DIAS), Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS), and DIAS-II trials [21]. A new trial (DIAS-III) was stopped because of lack of efficacy in the desmoteplase-treated patients. The thrust of this study was to determine whether the window for fibrinolytic therapy could be extended beyond 3 h [22].

Drugs under investigation

The success of plasminogen activators is, at least in part, highly dependent on the amount of plasminogen in the thrombus. Newer drugs do not depend on the availability of plasminogen.

Ancrod (Viprinex; Neurobiological Technologies, Emeryville, CA, USA) is a defibrinogenating agent derived from the venom of the Malayan pit viper. By defibrinogenating blood an anticoagulant effect is promoted. To study the safety and efficacy of ancrod in patients with acute ischemic stroke administered within 6 h of stroke onset, the Ancrod Stroke Study was performed. No significant difference in overall mean scores on the Scandinavian Stroke Scale could be demonstrated. Those patients with ancrod-induced 6-h fibrinogen levels of 130 mg/dL or less had a marginally significantly better neurological outcome on the Scandinavian Stroke Scale, mortality, and Barthel Index than ancrod-treated patients with higher fibrinogen levels [23].

V10153 (Vernalis, Winnersh, UK) is a novel modified recombinant variant of human plasminogen, which is activated to plasmin by thrombin. Thrombin, as the key enzyme involved in blood clot formation, is utilised to initiate clot destruction [24]. V10153 selectively induces lysis of newly formed clots, which should result in a reduced risk of hemorrhage. The V10153 Acute Stroke

Thrombolysis Trial (VASTT) was a phase II dose-escalation multicenter study. The trial has been halted because of significant hemorrhagic complications. The trial enrolment is closed and data are currently being analyzed.

Microplasmin (ThromboGenics, Heverlee, Belgium) is a truncated form of plasmin that is more resistant to antiplasmin. In a rabbit stroke model, IV microplasmin infusion resulted in a high rate of clot lysis without increasing the rate of ICH [25]. These findings were confirmed in the MITI-IV (Microplasmin in Treatment of Ischemic Stroke-IntraVenous) trial, a phase II multicenter, randomized, double-blinded, placebo-controlled ascending-dose clinical trial. Data are yet to be published.

Adjuvant drugs

Because fibrinolytic agents also have prothrombotic properties, early reocclusion has been demonstrated in 34% of the patients treated with IV rtPA [26]. Therefore, the adjuvant use of antithrombotic agents is common practice.

IV heparin for systemic anticoagulation during the periprocedural phase of endovascular stoke therapy is controversial. The potential advantages, including augmentation of the thrombolytic effect, prevention of acute reocclusion and reduction in the risk of catheter-related embolism, have to be weighed against the potentially increased risk of ICH when heparin is combined with a thrombolytic agent [12].

The use of *glycoprotein (GP) IIb/IIIa antagonists*, such as ReoPro (abciximab – an intravenous platelet aggregation inhibitor, is a monoclonal antibody directed against the platelet glycoprotein GP IIb–IIIa receptor), Integrilin (eptifibatide), or Aggrastat (tirofiban) in ischemic stroke remains investigational. In pilot studies, no major ICH was seen in combination with standard rtPA therapy [27]. Conversely, the AbESTT (Abciximab in Emergent Stroke Treatment) Trial-II, a phase III study, evaluating the safety and efficacy of abciximab in acute ischemic stroke, including patients who awoke with stroke symptoms, was permanently stopped owing to a high rate of intracranial hemorrhage in the abciximab-treated patients [28].

The data for the use of GP IIb/IIIa inhibitors in conjunction with intraarterial thrombolysis are limited to case reports. The number of cases with symptomatic ICH varied between 0 and 23% [6].

Endovascular therapy of acute stroke

The relatively high haemorrhage rates, in combination with the low complete recanalization rates, demonstrate the imitations of treatment solely with pharmacological agents. Especially in carotid terminus or basilar artery occlusions with large clot burden, the procedure takes time and may not achieve meaningful recanalization. Platelet-rich clots, old clots and calcified clots or fat emboli cannot be addressed. These factors substantiate the assumption that faster and more complete reperfusion will lead to better long-term outcomes for acute stroke patients.

Endovascular therapy promises higher recanalization rates because of the obvious advantages over IV rtPA, which are site specific, reduction of drug amount and potentially longer treatment windows. Nevertheless, the potential benefit of endovascular therapy must be weighed against the potential risk of the procedure. Intraarterial (IA) stroke therapy has been associated with a 5–7% risk for clinically significant procedural complications [12,13] and a 6–15% risk for symptomatic ICH [29,30].

Patients with minor strokes, who are treated with IV rtPA, have an 82% chance of a good outcome and the risk of symptomatic hemorrhage and death is 3% and 1%, respectively [31]. Such patients are quite unlikely to benefit from endovascular stroke therapy, as they often show no vessel occlusion on cerebral angiograms [32]. Most stroke centers offer IA stroke therapy only to patients with major strokes.

Different strategies of endovascular therapy are offered to reach reperfusion of occluded vessels in acute stroke. Most techniques focus on removing and dissolving the occlusive thrombus to reestablish antegrade flow, but some use the collateral vessel system of the brain to augment flow retrogradely. The different interventional methods are summarized in Table 2.

Intraarterial thrombolysis

The major theoretic advantage of IA thrombolysis over IV thrombolysis is that microcatheter techniques allow direct access to the occluded intracranial vessel and by penetrating the thrombus with the microcatheter the fibrinolytic agent can be infused into the thrombus. This permits a smaller dose of fibrinolytic agent to reach a higher local concentration than reached by systemic infusion and ideally allows more complete recanalization. Additionally,

TABLE 2

Strategies of endovascular stroke therapy.

Interventional method	Endovascular device used	Reperfusion	
		Antegrade	Retrograde
Intraarterial thrombolysis	Microcatheter	×	
Mechanical thrombus disruption	Microguidewire, laser	×	
Percutaneous transluminal angioplasty	Microcatheter with balloon for dilatation		
Aspiration of thrombus	Guiding catheter	×	
Endovascular thrombectomy	Clotretriever	×	
Augmented fibrinolysis	Ultrasound	×	
Thrombus entrapment	Stent	×	
Temporary endovascular bypass	Stent	×	
Flow augmentation	Balloon catheter		×
Transarterial or transvenous retrograde reperfusion	Balloon catheter		×

complications from systemic fibrinolytic effects, including ICH, can theoretically be reduced. Thus, the treatment window for endovascular techniques can be extended beyond the typical IV window of 3–6 h, which is important because of the low number of patients who present during the 3-h time window [32,33].

The first reports about IA administration of thrombolytic agents, mainly in the posterior circulation, were published in the 1980s. An overall recanalization rate of 60% and a mortality rate of 90% in nonrecanalized patients versus 31% in at least partially recanalized patients were found [34,35].

Multiple non-randomized case series reported successful use of IA thrombolysis. A review of patients treated with urokinase, showed recanalization rates of >75% when additional endovascular techniques (such as mechanical fragmentation of the thrombus, thromboaspiration, percutaneous transluminal angioplasty, and implantation of stents) were used [6].

Combined IV and IA thrombolysis

Several studies have evaluated the feasibility, safety and efficacy of combined IV rtPA with IA thrombolysis in patients with acute stroke. This approach has the potential of combining the advantages of IV rtPA (fast and easy to use) with the advantages of IA therapy (directed therapy, titrated dosing, mechanical aids to recanalization and higher rates of recanalization), thus improving the speed and frequency of recanalization.

In the Emergency Management of Stroke (EMS) Bridging Trial, no difference in the 7–10-day or 3-month outcomes between the IV rtPA or IV placebo followed by immediate intraarterial therapy with rtPA group were found, but there were more deaths in the IV/IA group [36].

The Interventional Management of Stroke (IMS I) Study investigated a combined IV and IA approach to recanalization in patients with ischemic stroke [37]. The 90-day mortality rate in IMS I subjects (16%) was numerically lower, but not statistically different from the mortality rate of the placebo (24%) or rtPA-treated subjects (21%) in the NINDS-rtPA-Stroke-Trial.

Intraarterial mechanical therapies

The limitations to IA lysis are related to clot characteristics. The response to the pharmacological agent may vary according to the source and type of clot. White platelet rich clots are more resistant to lytics than fresh red blood cell rich clots. De novo cardiac clots and paradoxial venous clots respond better than calcified clots from atherosclerotic plaques.

The therapeutic approach concerning these limitations changed dramatically in 2004 with the US Food and Drug Administration approval of the first mechanical clot-retriever [38]. The mechanical fragmentation of a clot increases the surface area accessible to fibrinolytic agents thus increases the speed of thrombolysis. The use of chemical thrombolytics is lower, or can be avoided, particularly in patients with contraindications to thrombolytic therapy. The treatment window can be exceeded beyond the limit of 6–8 h. Clot-retrieval devices also may be more efficient in catching mature embolic clots and emboli composed of cholesterol, calcium or other debris from atherosclerotic lesions [29,38,39].

The disadvantages of the mechanical approaches include the difficulty of navigating devices into the intracranial circulation, excessive trauma to the vasculature (potentially leading to vasospasms, vessel dissection, perforation or rupture) and fragmented thrombus causing distal embolization into previously unaffected territories.

Mechanical thrombus disruption

Several techniques are used for mechanical clot disruption. The most common is probing the thrombus with a *microguidewire*. This technique appears to be useful in facilitating chemical thrombolysis [40].

Alternatively, a *snare* (e.g., Amplatz goose-neck microsnare, Microvena) can be used for multiple passes through the occlusion to disrupt the thrombus [40]. A snare can also be used for clot-retrieval, mostly in situations in which the clot has a firm consistency or contains solid material.

Two devices that use laser technologies have been used to disrupt intracranial clots. The *EPAR* (Endovasix, Belmont, CA, USA) is a mechanical clot-fragmentation device based on laser technology. The photonic energy is converted to acoustic energy at the fiberoptic tip through creation of microcavitation bubbles, causing emulsification of the thrombus which is a mechanical thrombolysis and not a direct laser-induced ablation. In a pilot study with 34 patients, vessel recanalization occurred in 61.1%. There were ICHs in 5.9% and the overall mortality rate was 38.2% [41].

The *LaTIS laser device* (LaTIS, Minneapolis, MN, USA) uses the slow injection of contrast material as a 'light pipe' to carry the energy from the catheter to the embolus. A safety and feasibility trial was stopped because the device could not be deployed to the level of the occlusion in 2 of the first 5 patients.

Percutaneous transluminal angioplasty

The feasibility and high efficacy of percutaneous transluminal angioplasty (PTA) in acute stroke has been shown [42]. Partial or complete recanalization could be achieved in 91% of patients treated with direct PTA versus 64% treated with thrombolytic therapy alone. ICH was seen in 3% versus 19%, and good outcome occurred in 73% versus 50% of the patients, respectively [43]. 92% recanalization was achieved with the use of balloon angioplasty and adjuvant low-dose eptifibatide and/or thrombolytics with 42% good outcomes [44].

PTA may also be particularly useful in the cases of atherothrombotic disease, in which the residual stenosis may reduce flow sufficiently to lead to rethrombosis [16].

Endovascular thromboaspiration

The use of large 7 to 8-F guide catheter with syringe suction is a simple approach that has been used to remove occlusive thrombus and restore flow in symptomatic acute internal carotid artery occlusion. The guide catheter is slowly withdrawn to facilitate more complete removal of the thrombus [45].

Suction thrombectomy or thromboaspiration through either a microcatheter or a guiding catheter may be an option for a fresh clot. Aspiration devices cause fewer embolic events and vasospasm, but can be difficult to navigate into the intracranial circulation.

The *Penumbra System* (Penumbra, Alameda, CA, USA) uses a microcatheter and a separator, which is advanced and retracted

through the catheter to dislodge the clot and a suction device removes it. This system was initially tested in a pilot trial, where 23 subjects were enrolled. Recanalization before IA lysis was achieved in all treated cases (48%). Good outcome at 30 days was demonstrated in 45% of patients. The mortality rate was 45%. The use of adjunctive IA thrombolytic therapy was associated with a higher incidence of hemorrhage [46].

The *Angiojet* (Possis Medical, Minneapolis, MN, USA) is an endovascular rheolytic thrombectomy device that combines local vortex suction, created by high-pressure saline jets, with mechanical disruption. The generated clot fragments are then sucked into the 4- or 5-F access catheter, which is not flexible enough to allow its navigation into the intracranial arteries. The *NeuroJet* (Possis Medical) has been designed specifically for intracranial navigation. Unfortunately, vessel dissections and the inability to navigate through the carotid siphon were noted in a pilot study, and the trial was discontinued [47].

Endovascular thrombectomy

Endovascular thrombectomy means the extraction of the thrombus with the help of an endovascular tool through a catheter, and should provide rapid recanalization and flow restoration with a reduced risk of distal embolic complications. It is used alone or in conjunction with thrombolytic drugs. The limitations of these devices are intracranial navigation and capture of thrombus within the tortuous cerebral vasculature, and the risk of vessel wall damage or perforation. Some of the devices grasp the thrombus and apply force proximally; others are basketlike devices and use a distal approach to the clot.

The *Merci Retrieval System* (Concentric Medical, Mountain View, CA, USA) is a nitinol wire with an imprinted shape memory effect covered with a platinum coil to improve the visibility under fluoroscopy. It is inserted through a braided microcatheter to a position distal to the thrombus. After release from the microcatheter, it assumes a shape similar to a cork screw and has to be slowly pulled back under continuous aspiration via a balloon guiding catheter. More than 10,000 patients have been treated with this device. Currently the third-generation devices (V series) are used. With a 4.3F distal access catheter (DAC) an additional coaxial support can be added to the system, resulting in improved deliverability with the potential for simultaneous thromboaspiration or IA thrombolysis. The Merci embolectomy system has been studied in the MERCI and Multi MERCI trials, where a recanalization up to 55% of treatable vessels was reported, and in 68% after adjunctive therapy (IA rtPA, mechanical). Clinically significant procedural complications occurred in 5.5% and ICH in 9.8% of patients [29,38]. As an example how clot-retrievers are supposed to work the Merci retriever is shown in Fig. 1.

The *Phenox Clot Retriever* (Phenox, Bochum, Germany) is CE marked for the treatment of acute stroke in Europe since. It consists of a highly flexible nitinol/platinum-alloy compound core wire surrounded by a palisade of perpendicularly oriented stiff polyamide microfilaments trimmed in a conical shape. It is introduced into the target vessel through a microcatheter deployed distal to the thrombus and slowly pulled back under continuous aspiration via the guiding catheter. The smallest version of the device is used to recanalize distal MCA branches. Recently the second generation of the device (Phenox Clot Retriever CAGE), which incorporates a nitinol cage into the previous design, was constructed for the treatment of thrombi with firmer consistency. Recanalization was achieved in 56.3% of 45 patients with stroke with no device-related morbidity and mortality [48].

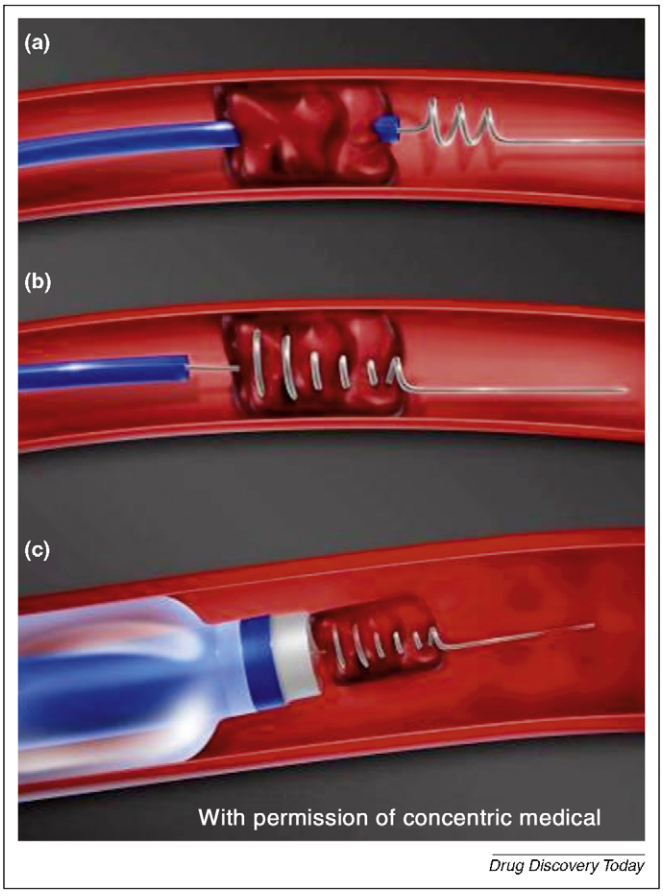

FIGURE 1

The principle of clot retrieving. The Merci System. Endovascular therapy for acute stroke is always performed under general anesthesia. First the Merci Balloon Guide Catheter is placed in the common or internal carotid artery for anterior circulation occlusion. Using standard cerebral catheterization techniques, a microcatheter is guided then through the guide catheter into the occluded vessel and passed beyond the thrombus **(a)**. The Merci Retriever is now advanced through the microcatheter, and several of the helical loops are deployed distal to the thrombus. The Merci Retriever is then retracted to the face of the thrombus, and the proximal loops are deployed within the thrombus **(b)**. The balloon of the Merci Balloon Guide Catheter has to be inflated now to arrest orthograde blood flow during removal of the thrombus. At least the Merci Retriever with the ensnared thrombus and the microcatheter are withdrawn together into the balloon guide catheter lumen. Continuous aspiration is applied to the guide catheter to promote complete evacuation of the thrombus **(c)**. Once a retrieval attempt is completed, the balloon of the balloon guide catheter is deflated to re-establish flow. If the clot could not be removed with the retriever, the procedure can be repeated up to 5 times.

The *Neuronet device* (Abbot Vascular, Temecula, CA, USA) has also been used successfully to retrieve intracranial clots. It is a microguidewire-based laser-cut nitinol basket open proximally with the crisscrossing basket portion tapering to a shapable platinum-tipped wire [49].

Very similar is the *Catch* (Balt Extrusion, Montmorency, France) device, a derivative of a self-expanding braided nitinol stent. It is a nitinol basket, closed at its distal end and anchored with a pair of

nitinol wires for insertion and withdrawal at the proximal end [50]. A comparison between the Merci and the Catch devices in an animal model has demonstrated superiority of the Merci retriever, which resulted in higher rates of overall recanalization (90% versus 70%), higher chances of recanalization at the first attempt, and a lower rate of thrombus fragmentation/distal embolization [51].

The *Alligator Retrieval Device* (Chestnut Medical Technologies, Menlo Park, CA, USA) is a retriever with 4 small grasping jaws attached to the tip of a flexible wire. This device has been used to treat 6 patients with intracranial clots (predominantly MCA), resulting in rapid clot removal and clinical improvement in all patients. In limited experience it provided a rapid, safe, and effective means for achieving revascularization [52].

The *In-Time Retriever* (Boston Scientific, Natick, MA, USA) has 4–6 wire loops and tends to bow when opened but has no specific opening to capture the embolus. This device has been successfully used in case studies [40].

The performance of 5 different embolectomy systems was recently evaluated using an *in vitro* pulsatile flow model. The Merci, Catch, and Phenox retrievers were equally able to mobilize and remove most thrombi, whereas the In-Time and Attractor devices achieved only partial thrombus removal at best, and with considerable difficulty during initial thrombus penetration and placement of the device [53].

Augmented fibrinolysis

The *MicroLysUS infusion catheter* (EKOS, Bothell, WA, USA) is a microcatheter with a piezoelectric element at its distal tip, which creates a microenvironment of ultrasonic vibration to facilitate thrombolysis. This is achieved by a combination of a noncavitating sonography, which reversibly separates fibrin strands, and acoustic streaming, which increases fluid permeation, resulting in increased drug-thrombus surface interaction. In a pilot study 14 patients were treated with IA rtPA or reteplase infusion through the EKOS microcatheter and simultaneous sonography transmission for $\leq$60 min. Recanalization was achieved in 57% of patients and good clinical outcome in 43%. The mortality rate was 36%. A comparison of angiographic outcomes between subjects treated in the IMS-II trial with the EKOS catheter and IMS-I subjects treated with the standard microcatheter demonstrated recanalization in 73% versus 56% respectively. This device is being investigated further in the IMS-III trial [6].

Thrombus entrapment

Stent placement of an acutely occluded intracranial vessel may provide fast recanalization by entrapping the thrombus between the stent and the vessel wall. This may be followed by thrombus dissolution via either endogenous or pharmacologic thrombolysis [6]. Treatment with balloon-expandable stents showed a recanalization rate of 79% and no symptomatic ICHs [54]. Multiple intracranial self-expandable stents are used in acute stroke therapy, although primarily designed for the treatment of wide neck aneurysms: the Neuroform (Boston Scientific), the Enterprise (Cordis, Miami Lakes, FL, USA), the LEO (Balt Extrusion, Montmorency, France) and the Solitaire/Solo stent (ev3 Endovascular, Plymouth, MN, USA). The Wingspan stent (Boston Scientific) is approved for the treatment of intracranial artherosclerotic lesions. Using these stents during stroke treatment, Gp IIb/IIIa inhibitors are administered intra- or immediately postprocedurally to avoid acute in-stent thrombosis. 82 Isolated case reports of successful intracranial recanalization with these stents have been reported [55,56]. The Pharos Vitesse stent (Micrus Endovascular), the only balloon-expandable stent approved for intracranial use, was used successfully in 4 patients with acute strokes (Killer M. *et al.*, unpublished).

The prospective 'First Food and Drug Administration-Approved Prospective Trial of Primary Intracranial Stenting for Acute Stroke' trial, called SARIS (Stent-Assisted Recanalization in Acute Ischemic Stroke) suggested primary intracranial stenting for acute stroke may be a valuable addition to the stroke treatment armamentarium [57].

Temporary endovascular bypass

The need for an aggressive antithrombotic therapy after stent implantation remains one of the major limitations to its use in acute stroke. However, the advent of closed-cell stents has allowed resheathing and removal of the stent after recanalization. The need for post-treatment dual antiplatelet therapy, which could potentially increase the risk of hemorrhagic conversion of the infarct, is not necessary. Recently the preliminary data about the use of the Solitaire/SOLO device as a temporary endovascular bypass and clot retriever were presented (Liebig T. *et al.*, unpublished). A clinical case in which partial deployment of an Enterprise stent resulted in immediate recanalization of an occluded MCA that was refractory to IV and IA rtPA, IA abciximab, and mechanical manipulation, confirmed this therapeutic concept [58].

The currently newest available device is the Trevo^{TM} System (Concentric Medical, Mountain View, CA, USA), an innovative, easy-to-use thrombus retrieval system. The main component of the Trevo System is a stentriever^{TM}, a new generation of retrieval devices which is able to restore flow in the occluded brain territory and remove the clot under aspiration with the guiding catheter. The first 24 cases, recently been performed in Europe, showed promising results (unpublished data). Fig. 2 shows an example of mechanical clot retrieving with the Trevo.

Alternative reperfusion strategies

The alternative reperfusion strategies use the collateral vasculature of the brain as well as retrograde and reversed flow.

Retrograde reperfusion and flow reversal are experimental treatment techniques that cause total reversal of the cerebral circulation and perfusion of the venous system with arterial blood into the capillary bed, which is then physiologically proximal to the occluded artery.

Flow augmentation

Global reperfusion or flow augmentation tries to increase cerebral blood flow (CBF) to perfuse the brain tissue distal to the occlusive thrombus via leptomeningeal collaterals. This retrograde reperfusion strategy may potentially lead to better recanalization rates when used as an adjunct to antegrade reperfusion treatments. The increase in CBF should result in the better delivery of thrombolytic drugs to the occlusion site, theoretically leading to better recanalization with systemic thrombolysis.

Flow augmentation can be achieved mechanically with the NeuroFlo device (CoAxia, Maple Grove, MN, USA). The NeuroFlo

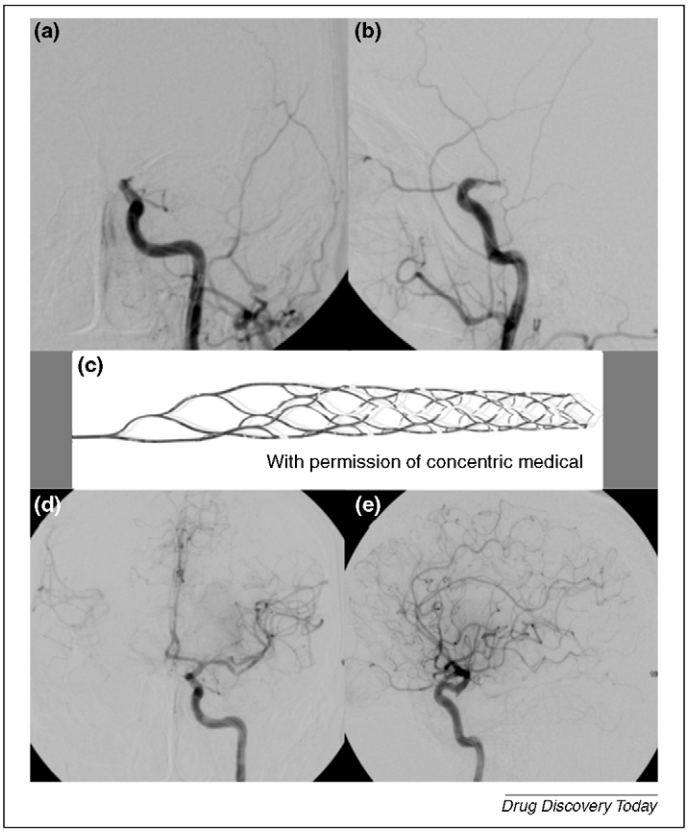

FIGURE 2

The Trevo™ System. 77-year-old female presented with stroke symptoms for 2 h. NIHSS at admission in the hospital was 18. After IV lysis as bridging therapy angiography showed a complete left sided ICA occlusion in ap **(a)** and lateral **(b)** view. The Guide Catheter was placed in the internal carotid artery for anterior circulation occlusion. Using standard cerebral catheterization techniques, a microcatheter was guided through the guide catheter into the occluded vessel and passed beyond the thrombus. The Trevo was now advanced through the microcatheter, and deployed from distal to proximal of the thrombus **(c)**. A control angiography showed flow in the occluded vessel. At least the Trevo with the ensnared thrombus and the microcatheter are withdrawn together into the balloon guide catheter lumen. Continuous aspiration was applied to the guide catheter to promote complete evacuation of the thrombus. After one pass with the Trevo the previously occluded territory is complete revascularized (**(d)** – ap view of the left ICA, **(e)** – lateral view of the left ICA).

device is a dual balloon catheter designed for partial occlusion of the aorta above and below the origin of the renal arteries. It is intended to increase blood flow to the brain and thus potentially reduce the damage caused by stroke. The recently completed SENTIS Phase III trial (Safety and Efficacy of NeuroFlo Technology in Ischemic Stroke) assesses the safety and efficacy of the NeuroFlo™ catheter for use in patients with ischemic stroke. The results are not yet published. Another ongoing 'Study to Evaluate the Effects of the Neuroflo Device in People Who Have Had a Stroke' investigates the feasibility and safety of the NeuroFlo™ in patients with persistent arterial occlusion after attempted thrombectomy with the Merci® Retriever System.

Limitations

Delayed symptomatic reocclusion after initial endovascular stroke therapy can lead to sudden clinical deterioration and has been linked to poor clinical outcomes [59]. The rate of reocclusion after endovascular treatments is 18% [60]. This may be underestimated as many patients present with large clinical deficits at time of presentation and explain the low rate of good clinical outcome despite of a high rate of revascularization.

Conclusions

The advantages of pharmacological thrombolysis over mechanical means are: The drugs are easier to administer and – 'Time is Brain': they can be started faster. Future newer generation lytics and platelet inhibitors may be even more faster, effective and specific. The disadvantages are that often no success can be achieved, and although the therapy can be initiated quickly, the effect occurs slowly and the risk of local and systemic hemorrhagic complications is evident.

The major disadvantages of an invasive procedure are additional risks and high costs compared with IV rtPA that are weighted against achieving higher reperfusion rates.

The current approach to acute endovascular stroke therapy is the use of mechanical clot-retrievers in combination with pharmacological agents. Future trials will address that and explore combined treatment strategies with neuroprotectants, antithrombotics, and supplementary mechanical strategies.

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