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Mechanical thrombectomy: Stent retrievers vs. aspiration catheters

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SOUHRN

Mechanická trombektomie ve spojení se systémovou trombolýzou představuje v současnosti standard léčby akutních ischemických cévních mozkových příhod (CMP). Mechanická trombektomie prodlužuje terapeutické okno nejméně o osm hodin od nástupu symptomů a účinněji než systémové podání trombolytik odstraňuje krevní sraženiny nereagující na jejich rozpouštění enzymy. U pacientů s různými kontraindikacemi systémové trombolýzy jde i o přijatelnou alternativu. Léčba pacientů s akutní ischemickou CMP formou mechanické trombektomie zvýšila úspěšnost revaskularizace a zároveň zajistila lepší klinické výsledky než farmakoterapie v kombinaci s intravenózní aplikací trombolytik. Použití zařízení (první generace) pro trombektomii, zvláště Merci Retrieval system (Stryker, Kalamazoo, MI, USA) a Penumbra aspiration system (Penumbra Inc., Alameda, CA, USA), sice zajistilo vyšší úspěšnost revaskularizace velkých mozkových tepen s uzávěrem, ne však nutně vyšší hodnoty příznivých klinických výsledků. Proto byla zařízení druhé generace, známá jako stent-retrievery, vyvíjena a konstruována s cílem dosáhnout rychlejší revaskularizace cév s uzávěrem a vyšších hodnot příznivého klinického výsledku. Studie prokázaly vyšší účinnost stent-retrieverů, hlavně Solitaire (ev3/Covidien, Irvine, CA, USA) a Trevo (Stryker) oproti zařízením první generace ve smyslu lepších hodnot příznivých klinických výsledků. Velmi slibný přístup představuje i odsávání (aspirace) trombů, ať již v kombinaci se stent-retrievery, nebo samotné. Několik randomizovaných kontrolovaných studií z poslední doby navíc prokázalo u pacientů s akutní CMP příznivější klinické výsledky farmakoterapie v kombinaci s mechanickou trombektomií za použití stent-retrieverů oproti samotné farmakoterapii. Uvedené klinické studie rovněž prokázaly relativně vyšší bezpečnost mechanické trombektomie za použití stent-retrieverů ve srovnání s optimální farmakoterapií.

ABSTRACT

Mechanical thrombectomy, in conjunction with systemic thrombolysis, is currently the standard of care for the treatment of acute ischemic stroke. Mechanical thrombectomy extends the therapeutic window up to at least 8 hours from the time of symptom onset and is more efficient than systemic thrombolytic agents in removing clots resistant to enzymatic degradation. It is also a viable option for patients with various contraindications against the use of systemic thrombolysis. Treatment of patients with acute ischemic strokes

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using mechanical thrombectomy devices has yielded both higher rates of revascularization as well as superior clinical outcomes when compared with medical therapy with intravenous thrombolytics alone. The use of first-generation thrombectomy devices, most notably the Merci Retrieval system (Stryker, Kalamazoo, MI, USA) and the Penumbra Aspiration device (Penumbra Inc., Alameda, CA, USA), achieved high rates of revascularization of occluded large cerebral vessels but did not necessarily result in high rates of favorable clinical outcomes. Second-generation devices, known as stent retrievers, were therefore created with the goal of achieving faster revascularization of occluded vessels and improved rates of favorable clinical outcomes. Stent retrievers, most notably the Solitaire (ev3/Covidien, Irvine, CA, USA) and the Trevo (Stryker), were shown to be superior to first-generation devices in terms of achieving higher rates of favorable clinical outcomes. Aspiration combined with stent retrievers or alone has also shown great promise. Moreover, several recent randomized controlled trials have demonstrated the superiority of medical therapy with mechanical thrombectomy using stent retrievers over medical therapy alone in achieving good clinical outcome in acute stroke patients. These clinical trials also demonstrated the relative safety of mechanical thrombectomy with stent retrievers compared to the safety of best medical therapy.

Introduction

The last decade has witnessed rapid and significant advancement in the treatment of acute ischemic stroke, turning it from a purely neurological disease treated with systemic thrombolytic medications into an interventional condition treated with mechanical thrombectomy and in situ vessel revascularization. Mechanical thrombectomy is currently used either as an adjunctive therapy along with intravenous (IV) thrombolytic agents or as a stand-alone treatment modality for acute ischemic strokes. Mechanical thrombectomy has a number of advantages over systemic thrombolysis. Firstly, it extends the therapeutic window beyond the 4.5-hour guideline for thrombolytics, with many trials using 8 hours from the time of symptom onset as the therapeutic window for mechanical thrombectomy [1–4]. Secondly, mechanical thrombectomy is more efficient than systemic thrombolytic agents in removing clots resistant to enzymatic degradation, such as mature fibrin and cross-linked thrombi containing calcium or cholesterol crystals [2,5]. Finally, mechanical thrombectomy is a viable option for patients with various contraindications against the use of systemic thrombolysis. Overall, treatment of patients with acute ischemic strokes using mechanical thrombectomy devices has yielded higher rates of revascularization when compared with intravenous (IV) thrombolytic therapy [6–8]. The first-generation devices for mechanical thrombectomy included the Merci Retriever system (Stryker, Kalamazoo, MI, USA) and the Penumbra aspiration system (Penumbra Inc., Alameda, CA, USA). Second-generation treatment devices included endovascular stent-retrieval devices, such as the Solitaire (ev3/Covidien, Irvine, CA, USA) and the Trevo (Stryker).

First-generation mechanical thrombectomy devices

Merci clot-retrieval system

The initial first-generation mechanical thrombectomy device was the Merci Retrieval system, which was approved in 2004 by the United States Food and Drug Administration as the first mechanical thrombectomy device used in patients with acute ischemic stroke. The Merci Retrieval system has undergone multiple revisions since its initial approval. The first generation (X5 and X6) was comprised of a helically-tapered corkscrew-like catheter tip. The second generation (L4, L5, and L6) incorporated a helical coil at a 90°-angle with respect to the proximal catheter, along with added filaments. The third generation (V 2.0, V 2.5, and V 3.0) is a hybrid design of a non-tapered, non-angulated filamented helical coil, which allows for maximal clot retention. The helical coil is attached to a wire-pusher and delivered through a microcatheter [2]. The Merci Retrieval system is usually used in conjunction with a balloon guide catheter that carries a silicone balloon at its distal end. Inflating the balloon temporarily arrests anterograde flow in the carotid or vertebral arteries, thus allowing for aspiration during the clot-retrieval process [9].

The success of the Merci Retrieval system in achieving vessel revascularization has been demonstrated by several clinical trials. The Mechanical Embolus Removal in Cerebral Ischemia (MERCI) phase 1 trial was a pilot study consisting of 30 patients with occlusion of major cerebral arteries [3]. In that trial, the use of the Merci Retrieval system resulted in the revascularization of 43% of occluded vessels when used alone and 64% of occluded vessels when used as an adjunct therapy to IV thrombolysis. Fifty percent of the patients in that trial achieved significant recovery, defined as a modified Rankin Scale (mRS) score of ≤3. The 30-day mortality rate was 36%. The MERCI and multi-MERCI trials, which included 141 and 164 patients, respectively, showed similar results [8,10]. When the results of both studies were combined, 65% of patients demonstrated successful revascularization [2]. Good functional outcome, defined as an mRS score of ≤2, was achieved in 28% of patients [2]. In both trials, the rate of mortality for patients who underwent successful revascularization was 28%, compared to 53% for those in whom successful revascularization was not achieved. Logistic-regression analysis demonstrated a significant correlation between successful revascularization and favorable clinical outcome and lower mortality rates in both trials. In each of the two trials, concomitant use of IV tissue plasminogen activator (t-PA) increased the rate of successful revascularization from 63% to 73% [7,10]. The use of IV t-PA was also shown to decrease the rate of mortality in both trials (28% vs. 40%). However, it was not shown to significantly increase the percentage of favorable outcome (38% vs. 31%) [2]. In 2011, the results from 872 patients treated with the Merci system in a prospective multicenter open-label registry revealed successful revascularization (Thrombolysis in Cerebral Infarction [TICI] perfusion grade 2a, 2b,

or 3) in 80% of cases [11]. However, at 90-days, the rate of mortality was 33%; and only 32% of those who underwent revascularization with the Merci system achieved favorable outcome. Young age, low presenting National Institutes of Health Stroke Scale (NIHSS) score, successful vessel recanalization, and lack of intubation/general anesthesia during the procedure were predictors of good outcome.

Penumbra aspiration system

The other main first-generation mechanical thrombectomy device is the Penumbra aspiration system, which was approved by the United States Food and Drug Administration in 2008, when it was deemed to be substantially equivalent to pre-existing mechanical thrombectomy devices. This system is used to remove occlusive thrombi that are dislodged in large intracranial vessels. The aspiration process involves both clot fragmentation and clot aspiration through a special catheter. Initially, an aspiration catheter is advanced to the site of the occlusion and, possibly, even past the occlusive thrombus. A separator device is subsequently advanced through the aspiration catheter and moved in and out of the aspiration catheter while an electric pump is simultaneously providing negative pressure. In this manner, the clot is fragmented and the small fragments are then suctioned into the aspiration catheter and out of the system. Aspiration systems have the advantage of minimizing distal embolization of the clot, first by fragmenting the clot and then by providing negative pressure to suction its small fragmented portions.

The success of clot aspiration systems depends on a variety of factors. In the large Penumbra pivotal stroke trial, which involved the revascularization of 125 vessels in 125 patients with intracranial large vessel occlusive disease, 82% of the vessels were successfully revascularized to Thrombolysis in Myocardial Infarction (TIMI) grade 2 or 3 [1]. However, in spite of this high rate of successful revascularization, the 90-day mortality amounted to 33%. Increased risk of mortality was associated with NIHSS score >20 at presentation, internal carotid artery (ICA) occlusion, and history of stroke. Only 42% of patients achieved good clinical outcome at 30 days, defined as a ≥4-point improvement in NIHSS score or an mRS score of ≤2 at the time of discharge. Favorable outcome was also associated with presentation within 8 hours from symptoms onset. Postmarketing trials of the Penumbra aspiration system yielded similar results [12,13]. The newer generation of the Penumbra aspiration system achieved superior results compared to the initial generation. For instance, a revascularization rate of 91% was achieved with the new Penumbra 054 device compared to 82% in the initial Penumbra pivotal trial; and revascularization was achieved within a mean time of 20 min, compared to 45 min in the initial trial [14]. However, the risk of mortality was still elevated (26%), and only 35% of patients achieved good neurologic outcome, defined as mRS score ≤2 at 90 days.

Second-generation mechanical thrombectomy devices

With both the Penumbra and Merci Retrieval systems, high rates of revascularization of occluded large cerebral vessels were achieved, but the use of these devices did not necessarily result in high rates of favorable clinical outcomes [15]. Therefore, several second-generation devices were created with the goal of achieving faster revascularization of occluded vessels, ultimately leading to better clinical outcomes. These second-generation devices are known as stent retrievers. Stent retrievers are an extension of the technology involving the use of stents for the treatment of acute ischemic stroke. This technology started in 2006 with the first report of the use of coronary stents to successfully revascularize an acute occlusion of the middle cerebral artery [16]. However, because of the potential complications associated with the implantation of stents within the cerebral vessels, such as the risk of in-stent thrombosis and the required use of postprocedural antiplatelet therapy, the technology evolved over the years to include stents that were retrieved at the conclusion of the procedure. As a general rule, self-expanding stents (Fig. 1) are preferred over balloon-mounted stents, because they reduce the risk of barotrauma to the vessel wall, thus decreasing the risk of vessel dissection and rupture [17].

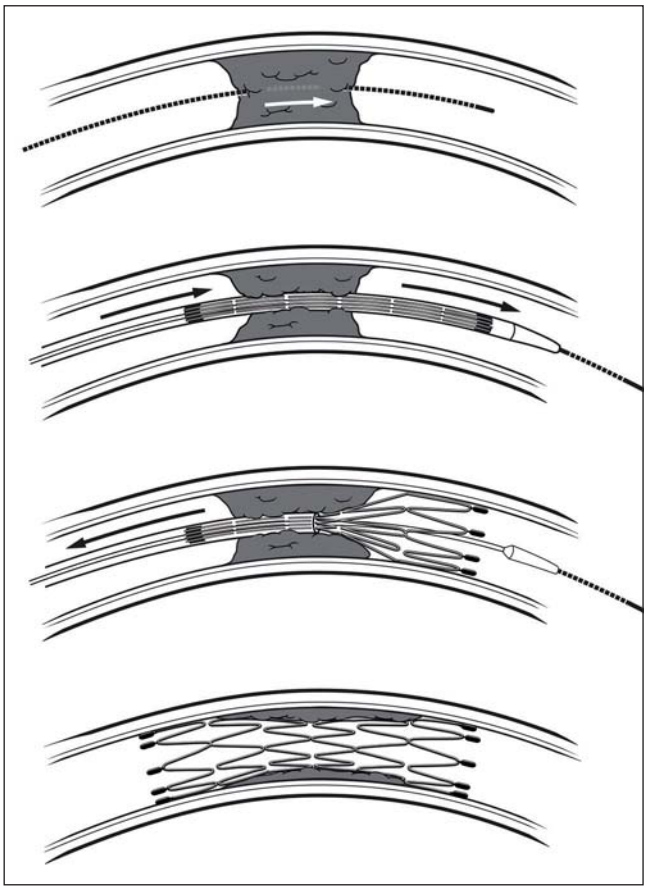

Fig. 1 – Deployment of expandable stent for the revascularization of large vessels with an occlusive thrombus. With permission from Levy et al. *American Journal of Neuroradiology* 28 (2007) 816–822.

Intracranial retrievable self-expanding stents currently used in the treatment of acute ischemic stroke include the Wingspan (Stryker Neurovascular, Fremont, CA), Neuroform (Stryker Neurovascular), Enterprise (Codman, Raynham, MA), Solitaire, and Trevo. Stents can be either partially recoverable (Enterprise) or completely recoverable

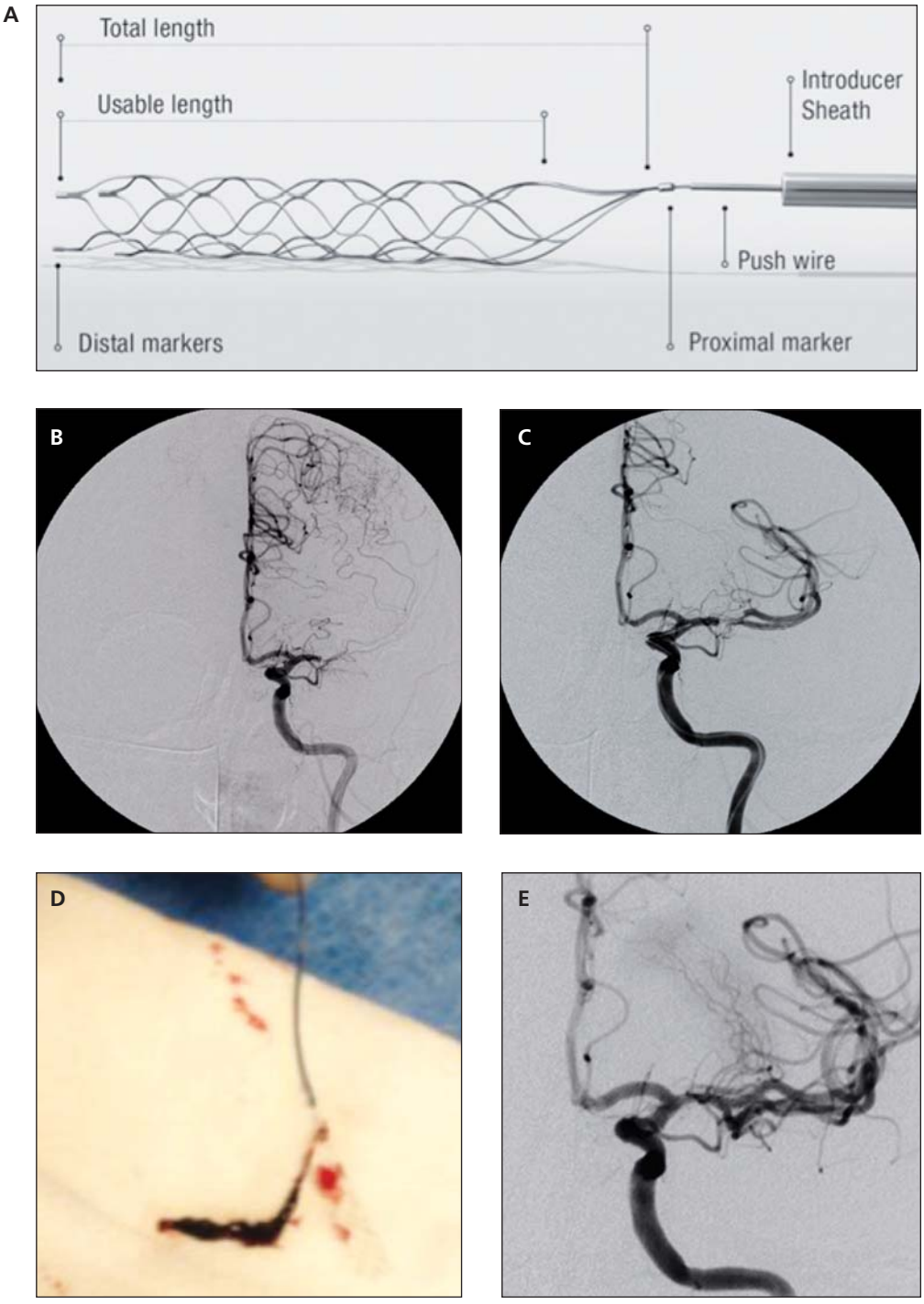

Fig. 2 – Acute stroke intervention utilizing the Solitaire FR device (ev3/Covidien) in a 57-year-old man. (A) The device is a self-expanding, nitinol system with closed cells and a longitudinal split, overlap design. Source: Machi et al. *Journal of NeuroInterventional Surgery* 4 (2012) 62–66. [*This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.*] (B) Diagnostic angiogram confirming occlusion of the M1 segment of the left middle cerebral artery. (C) Dual catheter-based angiography showing the length of the occlusive clot. (D) Retrieved emboli attached to the Solitaire device. (E) Final angiographic run showing recanalization of the left middle cerebral artery.

(Solitaire and Trevo stent retrievers). A stent retriever is a cylindrical device that consists of a self-expanding stent mounted on a wire and deployed within a catheter. Once at the site of the blood clot, the stent is released from within the catheter and self-expands within the thrombus. This immediately pushes the clot against the wall of the artery, thus instantaneously reestablishing blood flow to the brain in 80% to 90% of cases [17]. The stent is subsequently deployed for a few minutes, thus allowing ensnaring of the thrombus within the tines of the stent. The stent is then used to grab the clot; and as the wire is pulled back, the stent is retrieved back into the catheter,

and the thrombus is removed along with it. Retrieval of the stent eliminates the potential complications associated with permanent stent implantation, such as in-stent stenosis, jailing of branch vessels, and associated ischemia and the use of long-term antiplatelet therapy. Although most stents are completely recoverable, partially recoverable stents can be also employed in the treatment of acute ischemic strokes. Following partial deployment of these devices for 5–10 min in order to reestablish blood flow, the partially recoverable stents can be either retrieved under proximal aspiration through the guide catheter without recapture or, alternatively, they can be fully and permanently deployed to further push the thrombus against the vessel wall. If permanent deployment of the stent is planned, treatment with dual antiplatelet therapy must be instituted prior to the deployment.

The choice of stent depends on a variety of factors, including the interventionist's preference and level of comfort with the device. However, certain thrombi and atherosclerotic lesions are not amenable to treatment with stents. When choosing a stent, the interventionist must pre-measure the length of the thrombus and ensure that the stent will cover the entire length of the lesion, with a few millimeters of margin on each side. Newer stents, such as the Enterprise stent, are up to 37 mm in length. The vessel diameter must also be taken into consideration when choosing a stent, because various stents self-expand to different diameters. As a general rule, the diameter of the stent should be chosen based on that of the parent vessel just proximal to the occlusion [17]. This serves to increase the radial outward force of the stent against the distal occlusion.

Solitaire

Second-generation endovascular stent-retrieval devices have shown promising results in the rates of revascularization as well as in the establishment of a clear benefit with respect to clinical outcome [15]. Arguably, the most widely used stent retriever nowadays is the Solitaire device, which was approved for use in the United States in 2012 (Fig. 2). Several studies have compared the Solitaire to other revascularization technologies. The Solitaire Flow Restoration Device With the Intention for Thrombectomy (SWIFT) trial was the major trial comparing the Solitaire stentriever device to the Merci Retrieval system [18]. At the conclusion of the trial, 58 patients were treated with the Solitaire device and 55 were treated using the Merci system. Significantly more patients who underwent treatment with the Solitaire experienced vessel recanalization with no associated symptomatic intracranial hemorrhage (ICH) compared to those treated with the Merci system (61% vs. 24%; $p < 0.0001$). Moreover, good clinical outcome at 3 months (defined as an mRS score of ≤2 or equal to the pre-stroke mRS score if that score was >2, or an NIHSS score improvement of ≥10 points) was achieved more frequently with the Solitaire than with the Merci (58% vs. 33%; $p = 0.0001$). In addition, 90-day mortality was lower in the Solitaire group (17% vs. 38%; $p = 0.0001$). Major periprocedural complications occurred in 13% of the 144 patients enrolled in the SWIFT trial [19]. The rates of symptomatic ICH were higher with the use of the Merci system than the Solitaire device (11% vs. 1%; $p = 0.013$), as were the rates of symptomatic subarachnoid hemorrhage (7% vs. 1%; $p = 0.07$), air emboli (2% vs. 1%; $p = 1.0$), and distal emboli to new vascular territories (2% vs. 0%; $p = 0.38$). Alternatively, rates of certain complications were higher with the use of the Solitaire stent retrieval system than the Merci system, such as vessel dissection (5% vs. 2%; $p = 0.65$) and major groin complications (8% vs. 4%; $p = 0.48$). Another study demonstrated revascularization superiority of the Solitaire stent retriever compared to the Merci retriever as well as the Penumbra device [20].

The SWIFT trial showed that use of the Merci retriever was a predictor of the need for IV t-PA rescue therapy when vessel patency could not be restored, compared to stent retrieval with the Solitaire stent [21]. This translated into longer recanalization time, lower percentage of successful recanalization, and lower percentage of good outcome with Merci. Moreover, a post-hoc analysis of the trial results demonstrated that stent retrieval with the Solitaire device is associated with significantly lower rates of subarachnoid hemorrhage and symptomatic ICH than retrieval with the Merci system (2% vs. 13% and 1% vs. 11%, respectively) [22]. This difference was due to less frequent use of rescue therapy with intra-arterial t-PA. Postmarketing studies demonstrated that the use of the Solitaire device in clinical practice was comparable in performance to that reported in the SWIFT trial [23,24]. Interestingly, postmarketing studies have also shown that a variety of other endovascular techniques were used in the treatment of acute ischemic strokes in patients who underwent treatment with Solitaire stent retrieval (in up to 52% of cases in one study [23]). However, the complication rates associated with the use of the Solitaire device were higher in the postmarketing studies than in the clinical trials. For instance, one postmarketing study reported symptomatic ICH in 15% of patients within the first 24 hours and in-hospital mortality in 26% of patients [23].

Trevo

The Trevo is the other main stent retrieval device used in the setting of acute ischemic stroke (Fig. 3). This device was initially employed in Europe but eventually approved for clinical use in the United States in 2012. In the Thrombectomy REvascularization of large Vessel Occlusions in acute ischemic stroke (TREVO) study, which included 60 patients from 7 European centers, the overall rate of recanalization with the device was 92% [25]. Favorable neurological outcome, defined as mRS score ≤2, was reached in 55% of patients at 90 days, whereas the rate of symptomatic ICH was 5% and that of mortality was 20%. In a single-center study involving 50 patients with acute ischemic stroke treated with Trevo stentrievers, 61% achieved good clinical outcome within 90 days, defined as mRS score ≤2 [26]. Symptomatic ICH occurred in 12% of cases and the rate of mortality was 14% [26]. In the Trevo vs. Merci Retrievers for Thrombectomy Revascularization of Large Vessel Occlusions in Acute Ischemic Stroke (TREVO 2) trial, which randomized 88 patients to Trevo retrievers and 90 patients to Merci retrievers, a significantly higher rate of patients achieved reperfusion with TICI score of ≥ 2 in the Trevo group than the Merci group (86% vs. 60%, respectively; $p < 0.0001$) [27]. In addition,

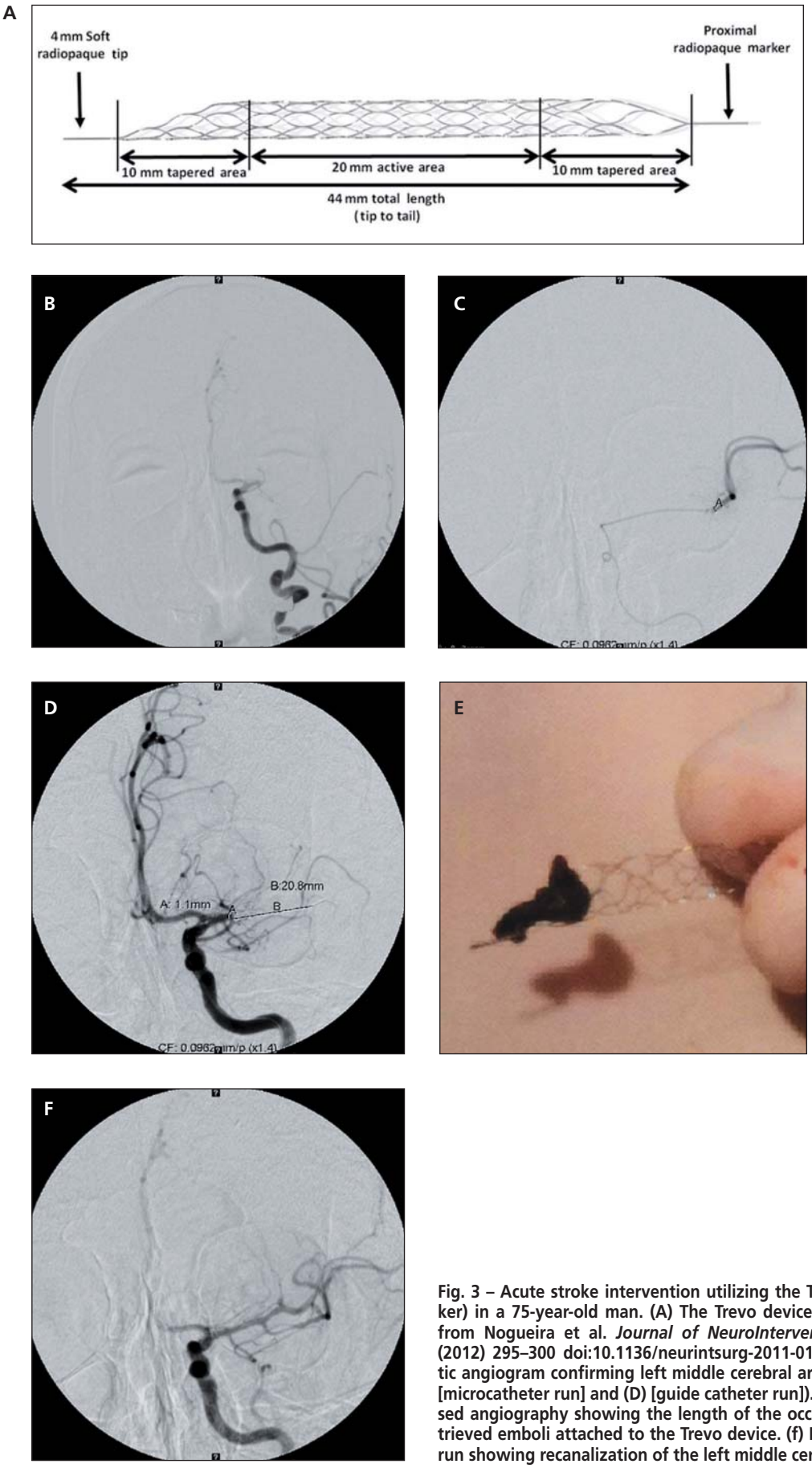

Fig. 3 – Acute stroke intervention utilizing the Trevo device (Stryker) in a 75-year-old man. (A) The Trevo device. With permission from Nogueira et al. *Journal of NeuroInterventional Surgery* 4 (2012) 295–300 doi:10.1136/neurintsurg-2011-01005. (B) Diagnostic angiogram confirming left middle cerebral artery occlusion, (C) [microcatheter run] and (D) [guide catheter run]). Dual catheter-based angiography showing the length of the occlusive clot. (e) Retrieved emboli attached to the Trevo device. (f) Final angiographic run showing recanalization of the left middle cerebral artery.

the use of adjunctive interventions of any kind was less common with the Trevo than with the Merci. Good long-term functional outcome, defined as mRS score ≤2 at 90 days, was higher with the Trevo stentriever than with the Merci retriever (40% vs. 22%, respectively). In that study, vessel perforation was more common with the Merci than with the Trevo, although the rates of symptomatic ICH were comparable between the two groups (7% for Trevo vs. 9% for MERCI). Mortality at 90 days was not significantly different between the two groups (33% for Trevo vs. 24% for MERCI; $p = 0.185$). Postmarketing studies have confirmed the safety and efficacy of the Trevo stentriever in patients with acute ischemic stroke. In one retrospective analysis of prospectively collected data, 89% of patients who had acute thrombectomy using the Trevo device achieved successful recanalization [28]. Good outcome, defined as mRS score ≤2, was achieved in 45% of patients. The rate of mortality was 19% at 90 days.

A relatively new generation of the Trevo stent retriever, the Trevo XP 3 mm × 20 mm retriever (known as 'Baby Trevo', Stryker Neurovascular), was recently developed for treatment of distal intracranial occlusions. In a study of 8 patients who underwent mechanical thrombectomy of 10 vessels using this technology, 5 had occlusions in the M3 branches of the middle cerebral artery, 3 had occlusions in the pericallosal and callosomarginal arteries, and 2 had occlusions in the P2 and P3 segments of the posterior cerebral artery [29]. All patients achieved complete recanalization of the target arteries using Baby Trevo, although there was a partial infarct in 5 of the territories supplied by these vessels and a complete infarct in 1. Two (25%) patients had postprocedural parenchymal hematomas. This technology shows promise for treatment of distal acute ischemic strokes, although application in a larger number of patients is necessary to validate its safety and clinical advantage.

Comparison of various stent-retrieval systems

Since the emergence of stent retrievers, several studies have been conducted to compare their efficacy and safety profiles. Generally speaking, the Trevo device showed a rate of success and a safety profile similar to those of the Solitaire. One recent meta-analysis comprised 20 of these studies involving the Solitaire (17 studies, n = 762) and the Trevo (3 studies, n = 210) [30]. According to this large meta-analysis, successful revascularization was achieved in 85% of cases and independent functional outcome was achieved in 51% of patients. The rate of mortality was 17%. In another large meta-analysis of 19 studies comprising 576 patients comparing the Solitaire and the Trevo thrombectomy devices, the safety profiles and rates of favorable outcomes were generally comparable between the two devices [31]. For instance, the rates of vessel revascularization (83% vs. 82% [revascularization was most commonly defined as TICI score of 2a to 3 or as TIMI score of 2 to 3]), the rates of good clinical outcome (51% vs. 47%), the rates of ICH (8% vs. 6%) and device-related complications (5% vs. 6%) were comparable between the Trevo and Solitaire devices, respectively. The only major difference in risk profile according to that study was double the rate of mortality with the use of the Trevo compared to the Solitaire (31% vs. 14%). In a prospective study of the two devices comprising 33 patients, the rates of vessel revascularization were similar between the Trevo group (77%) and the Solitaire group (60%) ($p = 0.456$), as were the rates of favorable outcomes (38% vs. 40%; $p = 0.435$) and 3-month mortality (30% vs. 25%; $p = 1.0$) [32].

First-generation versus second-generation thrombectomy devices

Multiple trials that compared first-generation clot aspiration devices to second-generation stent retrievers repeatedly demonstrated the superiority of the latter. For instance, in a prospective study of 122 acute ischemic stroke patients, successful recanalization was achieved in 82% of patients treated with stentrievers (Solitaire or Trevo) compared to 62% of patients treated with the Merci device ($p = 0.016$) [33]. Favorable clinical outcome at 90 days was achieved in 65% of patients treated with stentrievers compared to 35% of patients treated with the Merci ($p = 0.002$). The rate of ICH was also lower in patients treated with stentrievers than in those treated with the Merci (10% vs. 28%, respectively; $p < 0.01$). A large meta-analysis of 17 different primary studies demonstrated that although stent retrievers have a safety profile similar to that of the Merci device, treatment with either Solitaire or Trevo was associated with higher rates of recanalization ($p < 0.00001$) and better clinical outcomes at 90 days ($p < 0.0004$) [34]. Interestingly, however, the 90-day mortality rate was similar in both the Merci and the stent-retriever groups ($p = 0.70$). In another study of 315 patients with acute ischemic stroke who were treated with intra-arterial t-PA alone (127 patients), Merci clot aspiration (119 patients), or Solitaire or Trevo stent retrievers (69 patients), higher rates of complete vessel recanalization were observed with stent-retrieval technology than with the Merci device (67% vs. 57%, respectively) [35]. Time from groin puncture to final recanalization and time from groin puncture to initial flow restoration were both significantly shorter with the use of stentriever technology. Furthermore, higher rates of favorable outcome were achieved with the stent retrievers than with the Merci retriever (53% vs. 40%, respectively).

Stent retrievers and the most recent thrombectomy trials

Today, stent retrievers are considered to be the most advanced types of thrombectomy devices. Therefore, they were employed in several of the most recent randomized controlled trials comparing endovascular therapy to medical management of acute ischemic stroke. The most important and most recent of these trials are the Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN) [36], Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) [37], Solitaire With the Intention For Thrombectomy as

PRIMary Endovascular treatment (SWIFT PRIME) [38], Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-arterial (EXTEND-IA) [39], and the Randomized Trial of Revascularization with Solitaire FR Device vs Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset (REVASCAT) [40], all of which were published in 2015 in the *New England Journal of Medicine*. Although two of these trials, namely MR CLEAN and ESCAPE, allowed the use of other thrombectomy devices such as the Merci retrieval system, they still relied heavily on retrievable stents (97% and 86%, respectively) [36,37].

The first of these trials, MR CLEAN, was conducted at 16 medical centers in the Netherlands and enrolled a total of 500 patients [36]. The study demonstrated the superiority of neuroendovascular thrombectomy (mostly with stent retrievers) over medical therapy with IV t-PA, with a higher percentage of functional independence (mRS score ≤2) at 3 months in 33% of patients who underwent thrombectomy versus 19% of patients treated with IV t-PA. There were no significant differences in the rates of symptomatic ICH or mortality between the two groups. Following the release of these results, the 4 other aforementioned clinical trials were halted for early demonstration of efficacy in favor of mechanical thrombectomy.

The ESCAPE trial enrolled 316 patients at 22 centers worldwide [37]. The study investigators reported a significantly higher percentage of patients (53%) achieving functional independence (mRS score ≤2) at 90 days compared to patients who received only standard best medical therapy (29%; p <0.001). Furthermore, the rate of mortality was significantly lower in the group of patients treated with mechanical thrombectomy than in those treated with best medical therapy (10% vs. 19%; p = 0.04). The rate of symptomatic ICH was similar between the two groups.

The third trial, SWIFT PRIME, was conducted at 39 different centers and comprised 196 patients [38]. In this trial, thrombectomy with stent retrievers following IV t-PA thrombolysis was compared to medical therapy with IV t-PA alone. At 3 months, 60% of the patients in the thrombectomy group achieved functional independence, defined as mRS score ≤2, compared to 35% of the patients in the medical treatment-only arm (p <0.001). The two groups of patients did not exhibit significant differences in terms of mortality (9% for thrombectomy vs. 12% for IV t-PA alone; p = 0.50) or symptomatic ICH (0% for thrombectomy vs. 3% for IV t-PA alone; p = 0.12) at 90 days.

The EXTEND IA trial was similar in design to that of SWIFT PRIME, comparing IV thrombolysis followed by stent retrieval thrombectomy to IV thrombolysis alone [39]. The study randomized 70 patients at various centers in both Australia and New Zealand. Endovascular thrombectomy was shown to increase the rate of early neurologic improvement, defined as ≥8-point reduction in NIHSS score or score of 0 or 1 on day 3 (80% for mechanical thrombectomy vs. 37% for IV t-PA alone; p = 0.002). Stent retrieval thrombectomy was also shown to increase functional independence at 90 days (mRS score ≤2) (71% for mechanical thrombectomy vs. 40% for IV t-PA alone; p = 0.01). The two groups of patients did not exhibit significant differences in terms of the rates of death or symptomatic ICH.

The last of the trials is REVASCAT, which was conducted in Spain and compared mechanical thrombectomy with stent retrievers to standard medical therapy alone [40]. The study randomized 206 patients to each treatment arm over a period of 2 years. Thrombectomy with stent retrievers increased the rates of functional independence, defined as mRS score ≤2 at 90 days (44% for thrombectomy vs. 28% for medical therapy alone). Complication rates were not different between the two arms of the study, with a rate of death of 1.9% in both arms (p = 1.00) and a rate of symptomatic ICH of 18% in the thrombectomy group compared to 16% in the medical arm (p = 0.60).

When taken together, these 5 recent randomized controlled trials provide invaluable lessons about the best treatment practices for patients with acute ischemic stroke. Firstly, these trials repeatedly demonstrated the superiority of medical therapy with mechanical thrombectomy, the vast majority of which was performed with stent retrievers, over medical therapy alone in achieving good clinical outcome in acute stroke patients. Secondly, they reaffirmed that the best medical therapy is still a valuable tool in the armamentarium against acute stroke and that mechanical thrombectomy should be used in addition to, and not in place of, medical therapy in patients eligible for both techniques. Finally, these clinical trials demonstrated the relative safety of mechanical thrombectomy with stent retrievers compared to the safety of best medical therapy.

Predictors of clinical outcome following stent retrieval

Clinical outcome subsequent to stent-retriever thrombectomy for acute ischemic stroke depends on a variety of factors. In a recent study of 354 patients treated with stent retrievers at 24 different centers, poor clinical outcome and increased mortality were associated with age >80 years and higher NIHSS score at presentation [23,41]. Conversely, good outcome was associated with the use of IV t-PA, lower presenting NIHSS score, and shorter revascularization time [41].

Potential limitations of stent-retrieval technology

Despite their superiority in improving clinical outcomes in patients with acute ischemic strokes, stent retrievers are not without complications. In a recent study investigating the effect of these devices on blood vessels in rabbits, both the Solitaire and the Trevo devices were found to cause vascular damage that extends into the medial layer [42]. The Solitaire device was found to cause a significantly larger area of intimal thickening compared to the Trevo. The clinical significance of this finding remains to be investigated. Another disadvantage of this technology is that stent retrieval necessarily induces clot fragmenta-

tion, which may result in distal embolization and occlusion of previously uninvolved territory. To minimize the amount of released embolic debris, the stent should be deployed distal to the occlusion, thus trapping the debris between the stent and the vessel wall. A novel "distal" embolic protection device (Cover accessory device, Lazarus Effect, Campbell, California, USA) may help prevent clot fragmentation and embolization [43]. Another side effect of using stents in the treatment of acute ischemic stroke is acute in-stent thrombosis in cases where the stent is permanently left in place following successful recanalization. In that case, a half-systemic loading dose of a IIb/IIIa inhibitor, such as eptifibatide or abciximab, may be delivered intra-arterially via the guide catheter [17].

Conclusion

Mechanical thrombectomy carries multiple advantages over systemic thrombolytic therapy, although the use of both treatment paradigms is not mutually exclusive and has been shown to yield superior results compared to the use of either alone. Although first-generation mechanical thrombectomy devices showed promising rates of vessel recanalization, they did not demonstrate significant improvement in clinical outcomes. Conversely, second-generation mechanical thrombectomy devices, namely stent retrievers, were shown to be superior to the first-generation devices, particularly in terms of favorable clinical outcome. Due to these advantages, as well as their ease of use and rapid recanalization time, stent retrievers are currently the most frequently used mechanical thrombectomy devices in patients with acute ischemic strokes [17]. Mechanical thrombectomy with stent retrievers achieves superior clinical outcome in acute stroke patients compared to medical therapy alone. Moreover, stent retrievers have a safety profile similar to that of systemic thrombolytic therapy. The two main stent retrievers currently in use, namely the Solitaire and Trevo devices, are comparable to each other in terms of efficacy and safety profile. A new generation of stent retrievers, such as the Baby Trevo, has shown promising results in achieving thrombectomy in patients with occlusion of distal small vessels.

Contributions
Conception and design: both authors; Data acquisition: both authors; Data analysis and interpretation: both authors; Drafting the manuscript: Fanous; Critically revising the manuscript: both authors; Final approval of the manuscript: both authors.

Conflict of interest
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Ethical statement
The corresponding author declares, on behalf of all authors that the research was conducted according to Declaration of Helsinki.

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