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ENDOVASCULAR TREATMENT OF ACUTE ISCHEMIC STROKE

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Abstract:
Endovascular mechanical thrombectomy has revolutionized the treatment of acute ischemic stroke, extending the therapeutic window for intervention up to 24 hours in carefully selected patients. Recent multicenter randomized trials such as DAWN and DEFUSE-3 demonstrated that clinical condition and neuroimaging criteria—specifically, the infarct core volume (<70 mL) and ischemic tissue-to-core ratio (≥1.8)—are more critical than the time from symptom onset. The use of perfusion-based imaging processed with RAPID software has enabled precise identification of patients who benefit from revascularization. Endovascular treatment significantly improves functional outcomes and reduces mortality compared with standard therapy, confirming its efficacy and safety even beyond the traditional 6-hour limit.
Keywords: endovascular thrombectomy, ischemic stroke, DAWN, DEFUSE-3, perfusion imaging, RAPID software, therapeutic window.

ЭНДОВАСКУЛЯРНОЕ ЛЕЧЕНИЕ ОСТРОГО ИШЕМИЧЕСКОГО ИНСУЛЬТА

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Аннотация:
Эндоваскулярная механическая тромбэктомия произвела революцию в лечении ишемического инсульта, расширив терапевтическое окно вмешательства до 24 часов у тщательно отобранных пациентов. Многоцентровые рандомизированные исследования DAWN и DEFUSE-3 доказали, что решающую роль играют клиническое состояние и данные нейровизуализации — в частности, объем инфаркта менее 70 мл и отношение ишемизированной ткани к ядру ишемии ≥ 1,8. Применение перфузионных методик, анализируемых с помощью программного обеспечения RAPID, позволило точно определять пациентов, которым показана реваскуляризация. Эндоваскулярное лечение достоверно улучшает функциональные исходы и снижает летальность по сравнению со стандартной терапией, подтверждая эффективность и безопасность метода даже за пределами традиционного 6-часового окна.
Ключевые слова: эндоваскулярная тромбэктомия, ишемический инсульт, DAWN, DEFUSE-3, перфузионная визуализация, RAPID, терапевтическое окно.

O‘TKIR ISHEMIK INSULTNI ENDOVASKULYAR DAVOLASH

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Annotatsiya:
Endovaskulyar mexanik trombektomiya o‘tkir ishemik insultni davolashda inqilobiy o‘zgarishlar keltirib chiqardi, ehtiyotkorlik bilan tanlangan bemorlarda davolash oynasini 24 soatgacha kengaytirdi. DAWN va DEFUSE-3 kabi ko‘p markazli randomizatsiyalangan tadqiqotlar bemorning klinik holati va neyro-vizualizatsiya ko‘rsatkichlari — infarkt yadrosi hajmi (<70 ml) hamda ishemik to‘qima/yadro nisbati (≥1,8) — belgilovchi ahamiyatga ega ekanini ko‘rsatdi. RAPID dasturi yordamida qayta ishlangan perfuziya asosidagi tasvirlash usullari revaskularizatsiyadan foyda ko‘radigan bemorlarni aniq aniqlash imkonini berdi. Endovaskulyar davolash standart terapiyaga nisbatan funksional natijalarni yaxshilaydi va o‘lim darajasini kamaytiradi, usulning samaradorligi va xavfsizligini 6 soatlik an’anaviy chegara ortida ham tasdiqlaydi.
Kalit so‘zlar: endovaskulyar trombektomiya, ishemik insult, DAWN, DEFUSE-3, perfuziya tasvirlash, RAPID dasturi, terapevtik oyna.

Introduction. Ischemic stroke (IS) is a major medical and social problem. Its relatively high mortality, high rate of disability, and the need for prolonged hospital and post-hospital care make the treatment of such patients resource-intensive both for the healthcare system and the state as a whole. However, recent advances have made it possible to increase the number of favorable outcomes and the proportion of patients who regain independence.

Revascularization of cerebral arteries in the acute phase of IS through systemic thrombolysis, despite its limitations such as a short therapeutic window, a relatively low rate of successful recanalizations, and an extensive list of contraindications, has proven its effectiveness. The next stage in restoring blood flow in the affected cerebral artery was **mechanical thrombectomy using stent retrievers**. This method made it possible to extend the “therapeutic window” for revascularization and significantly improve its success rate. Advanced diagnostic and neuroimaging algorithms now allow for more accurate patient selection, which in turn increases the proportion of favorable outcomes. The method of **mechanical thromboaspiration** has also proven to be effective and safe, both in combination with stent retrievers and as a standalone technique.

Stages of Development of Thrombolytic Therapy in Ischemic Stroke. In 1983, **H. Zeumer et al.** [1] reported the first successful **recanalization of the basilar artery** after intra-arterial (endovascular) administration of **streptokinase**. During the 1980s, a series of experimental studies were conducted to identify the most effective thrombolytic agents for acute cerebral ischemia and to determine their optimal dosages [2, 3]. As a result, by the 1990s, **recombinant tissue plasminogen activator (rt-PA)** became widely used in clinical trials, with dosages ranging from **1.1 mg/kg** in the **ECASS** (European Cooperative Acute Stroke Study) trial to **0.9 mg/kg** in the **NINDS** (National Institute of Neurological Disorders and Stroke rt-PA Stroke Study) and **ECASS II** (The Second European Cooperative Acute Stroke Study) trials. Reducing the thrombolytic dose did not diminish its therapeutic effectiveness.

The results of the **randomized multicenter ECASS trial**, published in 1995, involved **113 patients**, of whom **57 (50.4%)** received rt-PA and **56 (49.6%)** received placebo. Outcomes in the thrombolysis group were statistically significantly better than in the placebo group, while **30-day mortality rates did not differ significantly** between the two groups [4].

The **NINDS trial** [5], whose results were also published in 1995, demonstrated that the probability of a favorable outcome **three months after the onset of ischemic stroke (IS)** was **50% higher** in the group receiving systemic thrombolysis with **0.9 mg/kg of recombinant tissue plasminogen activator (rt-PA)** compared to the control (placebo) group. A total of **624 patients** were randomized into two groups: **313 (50.2%)** received 0.9 mg/kg rt-PA, and **311 (49.8%)** received placebo. It was found that the **safe time window** for systemic thrombolysis using this protocol was a **3-hour “therapeutic window”** from symptom onset to the initiation of treatment.

In the **ECASS II study**, published in 1998, researchers attempted to **extend the therapeutic window to 6 hours**, but the rate of **hemorrhagic complications** proved significantly higher. Consequently, after this study, the **3-hour limit** for systemic thrombolysis remained unchanged [6]. However, **10 years later**, the **ECASS III (The Third European Cooperative Acute Stroke Study)** [7] demonstrated the **safety and efficacy of systemic thrombolysis within the first 4.5 hours** after symptom onset. This evidence led to the official extension of the therapeutic window to **4.5 hours** in European and American clinical guidelines.

In **2012**, the **IST-III (The Third International Stroke Trial)**, which enrolled **113 patients** (of whom **60 [53.1%] were over 80 years old**), did not show statistically significant differences in treatment outcomes across age groups, including patients aged 80 years and older [8]. Based on the work of **F. Mateen et al.** [9], published in 2009, which demonstrated that **thrombolytic therapy in patients older than 90 years is not advisable**, it can be summarized that systemic thrombolytic therapy with **rt-PA at a dose of 0.9 mg/kg** is effective **within a 4.5-hour therapeutic window** in patients **under 90 years of age**, provided there are no contraindications.

First Generation of Mechanical Thrombectomy Devices for Acute Cerebral Ischemia

Although the **first report of successful cerebral vessel revascularization in acute ischemia** described an **endovascular procedure with intra-arterial thrombolytic administration** via catheter into the vertebrobasilar system, the **endovascular method** was not routinely used in the treatment of acute IS for many years. Its **renaissance occurred only in the mid-2010s**. With technological advancements and the emergence of more sophisticated endovascular tools, attempts were made to **mechanically remove thrombi** from cerebral arteries in acute ischemic stroke.

However, for quite a long time, the use of **first-generation mechanical thrombectomy devices** for thrombus extraction did not yield the expected results. No breakthrough comparable to the introduction of systemic thrombolysis was achieved. Moreover, by **2013**, the results of **three randomized clinical trials** comparing **mechanical thrombectomy and systemic thrombolysis** in acute IS were published: **IMS-III** [10], **SYNTHESIS (Local versus Systemic Thrombolysis for Acute Ischemic Stroke)** [11], and **MR RESCUE (Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy)** [12].

In all of the previously mentioned trials, **first-generation thrombectomy devices** were predominantly used, and **none demonstrated a significant advantage** of mechanical thrombectomy over systemic thrombolysis. However, the emergence of **second-generation stent retrievers** fundamentally changed the landscape of endovascular stroke therapy. On **March 3, 2008**, in **Stuttgart, Germany**, **Dr. Hans Henkes** performed the **first endovascular cerebral thrombectomy** using a **self-expanding intracranial stent** with **electrolytic detachment** from the delivery system. The **Solitaire device** (*Medtronic, USA*) was initially designed for **stent-assisted coiling** of wide-neck intracranial aneurysms. Until the moment of detachment, the stent could be **repositioned** or **completely withdrawn** from the vessel, providing a major procedural advantage.

A distinctive feature of its design was the ability to **create a duplicate vessel wall layer** if the stent was deployed in a vessel narrower than its nominal diameter. Moreover, being originally engineered for the delicate treatment of complex intracranial aneurysms, the Solitaire stent possessed a **gentle structure with minimal vessel trauma risk**. These properties made it possible to **capture and remove the thrombus** safely, with a **low risk of arterial wall injury**.

Landmark Randomized Trials (2015): MR CLEAN and ESCAPE

Several **prospective randomized clinical trials** using **stent retrievers** like Solitaire were completed and published in **2015**, marking a new era in acute ischemic stroke management.

1. MR CLEAN (Multicenter Randomized Clinical Trial for Acute Ischemic Stroke in the Netherlands)

Published in **January 2015**, the MR CLEAN trial enrolled **500 patients** (of which **233 [46.6%]** underwent endovascular mechanical thrombectomy ± standard thrombolytic therapy, and **267 [53.4%]** received only standard thrombolytic therapy).

All participants had **ischemic stroke in the anterior circulation**, and **90%** received systemic thrombolytic therapy in both groups.

Results:

- Favorable outcomes (modified Rankin Scale [mRS] score 0–2):
  - **32.6%** in the endovascular group
  - **19.1%** in the control group
- **Mortality:** comparable between groups (18.9% vs. 18.4%)

These findings demonstrated a **clear superiority of endovascular treatment** in improving functional independence after acute ischemic stroke [13].

2. ESCAPE (Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke)

The **ESCAPE trial** compared endovascular treatment with systemic thrombolysis in **315 patients**: **165 (52.4%)** in the endovascular group and **150 (47.6%)** in the control group. The study included patients with anterior circulation strokes, but excluded those with **large ischemic cores** (based on CT perfusion) or **poor collateral circulation** (based on CT angiography).

The **therapeutic window was extended to 12 hours**, significantly beyond the standard 4.5-hour systemic thrombolysis limit.

Results (published February 2015):

- Favorable outcomes (mRS 0–2):
  - **53%** in the endovascular group
  - **29.3%** in the control group
- **Mortality:**
  - **10.6%** in the endovascular group
  - **19%** in the control group

The trial was **terminated early** due to the overwhelming superiority of the endovascular treatment arm. These data firmly established **stent retrievers as the new standard of care** in acute ischemic stroke therapy, expanding both the therapeutic time window and the likelihood of favorable outcomes [14].

Symptomatic intracranial hemorrhages occurred in **3.6%** of patients in the endovascular group and **2.7%** in the control group [14].

The **EXTEND-IA trial** (*Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection*), which randomized **70 patients**, was also **terminated early** due to the **clear superiority** of endovascular treatment. The study design included patients with **acute ischemia of the anterior cerebral circulation**, with an infarct core volume **<70 mL**, and a **therapeutic window of 6 hours** from symptom onset.

Results (February 2015):

- **Favorable outcomes (mRS 0–2):** 71% in the endovascular group vs. 40% in the control (systemic thrombolysis) group.
- **Mortality:** no significant difference between groups.

These findings confirmed the **clinical and radiological advantages** of patient selection based on perfusion imaging and demonstrated that thrombectomy significantly improves recovery outcomes [15].

SWIFT PRIME and REVASCAT Trials

Similar conclusions were reached in the **industry-sponsored SWIFT PRIME trial** (*Solitaire FR With the Intention For Thrombectomy as Primary Treatment for Acute Ischemic Stroke*), which randomized patients into two groups:

1. Endovascular thrombectomy using the **Solitaire device**, combined with or without intravenous thrombolysis;
2. A control group receiving **systemic thrombolysis only**.

The **SWIFT PRIME study** demonstrated that combining **Solitaire stent retriever thrombectomy** with systemic therapy dramatically improved outcomes in patients with anterior circulation stroke [16].

Another **manufacturer-sponsored study**, **REVASCAT** (*Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours*), expanded the **therapeutic window to 8 hours** and showed a **twofold higher rate of favorable outcomes** (mRS 0–2) in the endovascular group compared with the control group. Importantly, there

were **no significant safety differences**, confirming that the procedure was both **effective and well tolerated** [17].

Guideline Integration — 2015 ASA/AHA Recommendations

In **June 2015**, following the accumulation of high-quality evidence from the MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, and REVASCAT trials, the **American Heart Association (AHA)** and **American Stroke Association (ASA)** released **interim clinical guidelines**. These guidelines officially recognized **endovascular mechanical thrombectomy using stent retrievers** as a **first-line treatment** for eligible patients with acute ischemic stroke. At the same time, **systemic intravenous thrombolysis** remained **recommended in parallel** for patients **without contraindications**, emphasizing the complementary role of both approaches [18].

Endovascular Mechanical Thromboaspiration

In parallel with stent retriever technology, **endovascular mechanical thromboaspiration** was developed as an alternative or adjunctive method for recanalization.
For **safe and effective thromboaspiration** from cerebral arteries, the **aspiration catheter** must possess several critical — and technically challenging — design features:

- **Wide lumen** — to ensure effective aspiration and clot removal.
- **Soft, atraumatic distal tip** — to minimize vascular injury.
- **Excellent navigability** — to allow smooth advancement through **tortuous intracranial vessels**.
- **Strong proximal support** — to maintain stability during aspiration and clot extraction.

These requirements led to the emergence of specialized **large-bore aspiration systems** such as **Penumbra**, **ACE**, and later **AspiRE**, which enabled direct aspiration first-pass techniques (ADAPT) that further expanded the range of endovascular options in acute ischemic stroke therapy. The **ACE family of catheters (Penumbra, USA)** became the most widely used devices, as they effectively combined all the essential characteristics for safe and efficient thromboaspiration.

In **June 2016**, **B. Lapergue et al.** [19], in a **prospective non-randomized study**, demonstrated a **slight advantage** of the aspiration technique compared with stent-retriever thrombectomy. However, the **randomized, prospective, multicenter ASTER trial** (*Direct Aspiration First Pass Technique for Thrombectomy for Large Vessel Occlusion in Acute Ischemic Stroke*) [20] found **no statistically significant difference** between the two techniques. The rates of successful **revascularization (TICI 2b–3)** were **85.4%** for aspiration and **83.1%** for stent-retriever thrombectomy.

In clinical practice, most **stroke centers** now use **both mechanical approaches**, often **combining** them for optimal results. Modern **distal access catheters**, such as **Sophia** (*MicroVention, USA*) and **Fargo** (*Balt, France*), can serve **dual purposes** — providing **proximal support** during stent deployment and **simultaneous aspiration** during device retrieval.

Updated Guidelines — 2018 SNIS Recommendations

In **January 2018**, the **Society of NeuroInterventional Surgery (SNIS)** published **updated recommendations** for the management of **acute ischemic stroke (AIS)**. The document provided important clarifications regarding the **combination of mechanical thrombectomy and intravenous thrombolysis**:

- **Endovascular mechanical revascularization achieving TICI 2b–3** should be considered the **primary goal** of AIS treatment.
- Although **systemic thrombolysis alone** is usually **ineffective** in large-vessel occlusions, there is **no evidence of harm** when it is **combined with mechanical thrombectomy**.
- Given the **potential benefit** and **absence of clear harm**, **intravenous rt-PA** should be administered **whenever not contraindicated**, even if endovascular thrombectomy is planned.
- Importantly, **systemic thrombolysis should not delay** the initiation of the endovascular procedure [21].

Anesthesia and Technical Aspects of Endovascular Intervention. A key question in endovascular mechanical thrombectomy is the **choice of anesthesia**. There is **no universal**

consensus on whether to prefer **sedation** or **general anesthesia**. Some stroke centers favor **conscious or moderate sedation**, while others perform thrombectomy under **general anesthesia**.
W. Brinjikji et al. [22], in a **meta-analysis of 9 studies** including **1956 patients**, found **better outcomes** with **sedation** — including **lower mortality**, **higher rates of favorable outcomes**, and **fewer respiratory complications** compared with general anesthesia.
However, the **randomized SIESTA trial** (*Sedation vs Intubation for Endovascular Stroke Treatment*) [23], designed to clarify this issue, **did not reveal any statistically significant differences** between general anesthesia and sedation in terms of efficacy or safety.
The **ANSTROKE randomized trial (2017)** [24] found **no significant difference** in favorable outcomes between patients treated under **general anesthesia** and those under **conscious sedation** during endovascular stroke intervention. Consequently, both anesthesia modalities are considered **acceptable and appropriate**, and their choice may depend on **patient-specific factors** and the **established workflow of the stroke team**.

Technical Considerations — Balloon Guide Catheters

Another key technical aspect of endovascular thrombectomy is the **use of balloon guide catheters (BGCs)**. These devices allow **temporary cessation of antegrade blood flow** during thrombus retrieval, potentially **reducing the risk of clot fragmentation and distal embolization**.
In the major randomized multicenter trials — **MR CLEAN, EXTEND-IA, ESCAPE, SWIFT PRIME, and REVASCAT** — the use of balloon guide catheters was **not a mandatory requirement**. However, subsequent studies have demonstrated their **safety and efficacy**, indicating that BGCs may **shorten the time to successful revascularization** and **improve recanalization quality** in large vessel occlusions [25].

Beyond the Conventional Therapeutic Window — The DAWN and DEFUSE-3 Trials

In **January 2018**, the landmark **DAWN trial** (*DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late-Presenting Strokes Undergoing Neurointervention with Trevo*) was published. Sponsored by **Stryker (USA)**, the manufacturer of the **Trevo stent retriever**, this **randomized multicenter prospective study** evaluated the feasibility of **endovascular treatment beyond the traditional 6-hour therapeutic window**.
Eligible patients exhibited a **clinical–imaging mismatch** — that is, **severe neurological deficit with a relatively small infarct core**, and presented **6–24 hours** after symptom onset. Participants were randomized into two groups:

- **Standard medical therapy**, and
- **Endovascular thrombectomy using the Trevo device**.

Neuroimaging data — **MRI with diffusion-weighted imaging (DWI)** or **CT perfusion (CTP)** — were analyzed using **RAPID software** (*Ischemia View, USA*) to quantify infarct volume and viable tissue.

Results of the DAWN trial:

- Favorable functional outcome (mRS 0–2) was achieved in **49%** of patients in the endovascular group, versus only **13%** in the control group.
- Subgroup analysis demonstrated similar advantages across both time intervals:
  - **6–12 hours:** 54% (endovascular) vs. 19% (medical)
  - **12–24 hours:** 43% (endovascular) vs. 8% (medical)

These findings **redefined the upper time limits** for mechanical thrombectomy in selected patients, highlighting the role of advanced neuroimaging in **identifying viable penumbra beyond 6 hours** [26].
At the same time, the **DEFUSE-3 trial** (*Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke*) — conducted by the **U.S. National Institutes of Health (NIH)** — provided complementary evidence. This **prospective randomized multicenter study** compared **endovascular therapy** versus **standard medical management** in patients with acute ischemic stroke treated within a **6–16-hour window** from symptom onset. Its design mirrored DAWN's criteria, emphasizing **perfusion-core mismatch** as the key selection factor for late-presenting stroke candidates.

In the **DEFUSE-3 trial** [27], **patient selection** was based exclusively on **CT perfusion (CTP) imaging** parameters. The inclusion criteria required a **core infarct volume of less than 70 mL**, and an **ischemic tissue-to-core ratio of ≥ 1.8**, indicating a substantial amount of salvageable brain tissue (penumbra). All imaging data were processed using the **automated RAPID software** (*iSchemaView, USA*), ensuring standardized and objective measurement of perfusion-core mismatch.

Results. The study demonstrated a **clear superiority of the endovascular group** not only in terms of **functional outcomes**, but also in **mortality rates**. Outcomes were assessed **at 90 days (3 months)** after treatment:

- **Favorable outcome (mRS 0–2):**
  - **45%** in the endovascular thrombectomy group
  - **17%** in the standard medical therapy group
- **90-day mortality:**
  - **14%** in the endovascular group
  - **26%** in the control group

These results provided **compelling evidence** that endovascular mechanical thrombectomy significantly improves both **survival and neurological recovery** even **beyond the conventional 6-hour therapeutic window**, when patients are selected using advanced perfusion imaging criteria.

Clinical Implications and Paradigm Shift in Acute Stroke Management

The **latest randomized trials of 2018 (DAWN and DEFUSE-3)** collectively demonstrated that the **clinical condition** and **neuroimaging profile** of a patient are **more decisive** than the strict duration of ischemic symptoms in determining treatment eligibility.

Both studies conclusively proved the **efficacy and safety** of **endovascular mechanical thrombectomy** in appropriately selected patients **up to 24 hours** from symptom onset. This body of evidence prompted **global revisions** of clinical practice guidelines, emphasizing **individualized imaging-based selection** rather than rigid time-based exclusion.

Conclusion. Endovascular mechanical thrombectomy has become a cornerstone in the management of acute ischemic stroke, fundamentally transforming the prognosis of patients with large vessel occlusions. The evolution of endovascular technology—from first-generation retrieval devices to advanced stent retrievers and aspiration catheters—has dramatically improved rates of successful revascularization and functional recovery. Randomized multicenter trials such as **MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT, DAWN,** and **DEFUSE-3** have provided robust evidence that mechanical thrombectomy is both **effective and safe**, even beyond the traditional 6-hour therapeutic window, when guided by modern neuroimaging techniques such as perfusion CT or MRI analyzed with **RAPID software**.

These studies have shifted the paradigm of stroke management from a rigid time-based model to a **tissue-based approach**, where patient selection relies on identifying viable brain tissue rather than the duration of symptoms alone. Endovascular therapy not only improves survival but also significantly increases the likelihood of functional independence.

In summary, the integration of endovascular thrombectomy into comprehensive stroke care—alongside systemic thrombolysis when indicated—represents one of the greatest achievements in modern neurointervention. Continuous technological advancement, optimized patient selection, and multidisciplinary collaboration will further enhance outcomes and expand access to life-saving revascularization therapy worldwide.

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