

Systematic Review and Meta-Analysis

Stent Retriever Thrombectomy Potentially Increases the Recanalization Rate, Improves Clinical Outcome, and Decreases Mortality in Acute Basilar Occlusion: A Systematic Review and Meta-Analysis

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Keywords

Basilar artery occlusion · Intravenous thrombolysis · Thrombectomy · Meta-analysis · Systematic review

Abstract

Background: Acute basilar artery occlusion (BAO) is a devastating condition if untreated. The optimal treatment strategy, however, is unknown. Historically, interventional approaches have been favored over intravenous thrombolysis (IVT), although this is not supported by good evidence. The aim of this systematic review and meta-analysis was to summarize and compare the results for treatment modalities of BAO, namely, IVT and interventional stent retriever thrombectomy (SRT). **Methods:** Studies on IVT and SRT in BAO were systematically searched. Successful recanalization (TICI $\geq 2b$), favorable clinical outcome (modified Rankin Scale score ≤ 2), mortality, and the rate of symptomatic intracranial hemorrhage (SICH) were the target parameters. Only studies with ≥ 15 patients were included. IVT prior to SRT was allowed. Studies were excluded (1) if > 1 thrombectomy device was used in $> 50\%$ of the patients and (2) when data on outcome or treatment could not be parsed (e.g. registries). Odds ratios (ORs) were calculated using Mantel-Haenszel risk ratio estimation. Results are given as OR and the 95% confidence interval (95% CI). The χ^2 test was used to compare the outcome parameters clinical outcome, recanalization, mortality, and SICH. **Results:** A total of 17 studies (4 on IVT and 13 on SRT) with a total of 672 patients (IVT, $n = 314$; SRT, $n = 358$) were identified. Cumulatively, we found a highly significantly improved clinical outcome (43 vs. 31%, $p = 0.004$, OR [95% CI] = 1.66 [1.21, 2.76]), increased recanalization rate (88 vs. 60%, $p < 0.00001$, OR [95%

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CI] = 3.99 [2.73, 5.84]), and decreased mortality (26 vs. 41%, $p = 0.0004$, OR [95% CI] = 1.86 [1.33, 2.61]), as well as an equal rate of SICH (5 vs. 7%, $p = 0.15$, OR [95% CI] = 1.68 [0.82, 3.43]), in patients treated with SRT compared to those treated with IVT alone. **Conclusions:** The data from this meta-analysis suggest a possible superiority of SRT over IVT, pending positive results of randomized controlled trials. According to international recommendations, patients with BAO should preferentially be treated with SRT; if no contraindications exist, IVT should not be withheld.

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Introduction

Acute basilar artery occlusion (BAO) is a rare condition, accounting for only about 3% of all ischemic strokes [1]. Untreated, it is associated with >90% mortality and a high level of dependency among survivors [2, 3]. The primary goal of acute therapy is to reestablish blood flow in the basilar artery, which can be achieved through intravenous application of alteplase (intravenous thrombolysis [IVT]) or endovascular disruption of the thrombus (endovascular therapy [EVT]). Although there is a historically grown trend towards EVT [4], there is no good evidence that supports the assumption that EVT is superior to IVT. A previous meta-analysis failed to demonstrate a benefit in clinical outcome with EVT versus IVT [5]. However, EVT has substantially developed in recent years, and recanalization rates have dramatically improved. The advent of stent retrievers marked the current standard for stroke treatment in the anterior circulation, with recanalization rates of $\geq 80\%$ [6, 7].

The positive results of recent thrombectomy trials prompted us to perform this updated review, since a growing number of studies on BAO have been published. In this systematic review and meta-analysis, we want to summarize and compare the treatment of BAO with IVT and stent retriever thrombectomy (SRT). We hypothesized that SRT would not only increase recanalization rates but also improve clinical outcome.

Materials and Methods

Search Strategy and Data Collection

Using PubMed, we identified studies (published in final form) through June 2018 reporting on patients >18 years of age with acute BAO treated with SRT or IVT with alteplase as first-line treatment. IVT prior to SRT was allowed. Any additional treatment was allowed, but if it was applied in >50% of the patients in a study, the study was excluded. Both prospective and retrospective designs were allowed. Only studies reporting on ≥ 15 patients were included. If study groups published successive articles with accumulating numbers of patients, only the most recent publication was included. Stroke registries from which information on patients with acute BAO and/or outcome and/or specific therapeutic approach could not be parsed were excluded. Review articles, (conference) abstracts, experimental or animal studies, and articles lacking radiological or clinical data were excluded. As minimum information, data on (1) recanalization rate, (2) clinical outcome, and (3) mortality were required. Favorable outcome was defined as a score of 0–2 on the modified Rankin Scale (mRS) at a follow-up after discharge. Successful recanalization was defined as TICI (Thrombolysis in Cerebral Infarction) grades 2b–3. Some older studies did not adhere to these contemporary definitions of favorable outcome and successful recanalization. In these instances, the study definitions of favorable outcome and successful recanalization were kept, but this was explicitly stated.

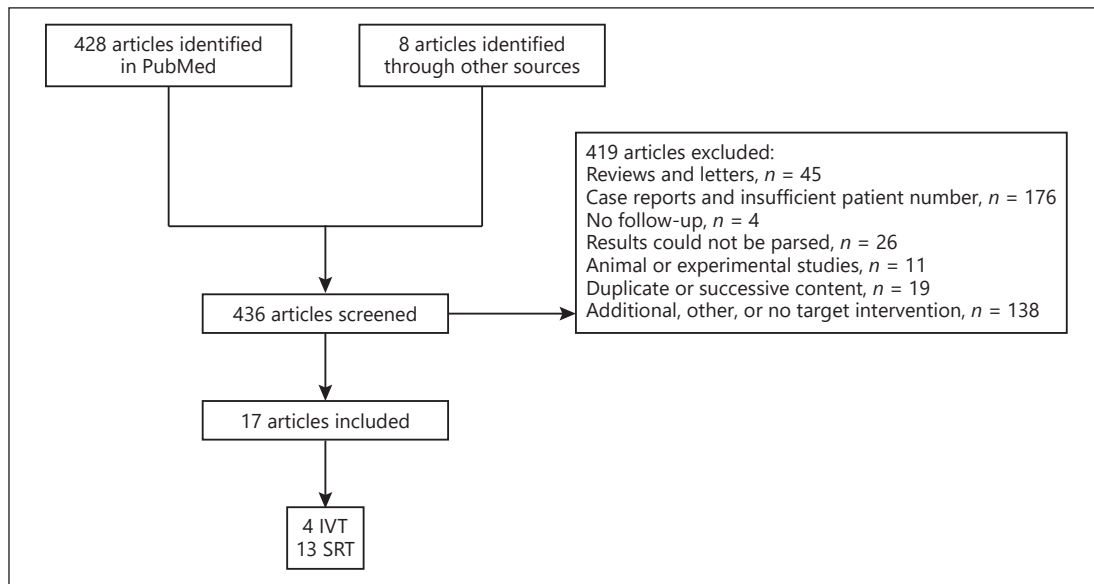


Fig. 1. Data collection. IVT, intravenous thrombolysis; SRT, stent retriever thrombectomy.

Two investigators (one board-certified radiologist and one board-certified neurologist) reviewed the studies and performed additional handsearching, e.g. of the literature sections of retrieved articles. If necessary, authors were contacted to obtain missing data. Data pertaining to the study design (study period, country where the study was conducted, and inclusion design), patient demographics (number of patients, age, and sex), and treatment-related information (treatment modality and additional treatment) were extracted and tabulated. Data pertaining to outcome parameters (recanalization rate, clinical outcome, mortality, and symptomatic intracranial hemorrhage [SICH]) were also extracted and tabulated. Subsequently, events, nonevents, and total numbers of cases in the respective category were extracted, calculated, and tabulated for each individual study and for the combined study population. Disagreement was resolved in consensus.

Statistical Analysis

Odds ratios (ORs) were calculated using Mantel-Haenszel risk ratio estimation. Results are given as OR and the 95% confidence interval (95% CI). The χ^2 test was used to compare the outcome parameters clinical outcome, recanalization, mortality, and SICH. I^2 statistics was used to express heterogeneity. The level of significance was set at $p < 0.05$. Continuous data are reported as mean \pm SD or median and range, categorical data as frequencies and percentages where appropriate. All calculations were made using Review Manager (version 5.3; The Cochrane Collaboration) and OpenMetaAnalyst (Tufts Medical Center, 2012).

Results

A total of 17 studies (4 on IVT and 13 on SRT) [8–24] with a total of 672 patients (IVT, $n = 314$; SRT, $n = 358$) were retrieved (see Fig. 1 for data collection). The data collection period ranged back to 1985 for the IVT group, while stent retrievers have only been used since 2009. The included studies had an overall preponderance of European centers. While in the IVT group no Asian studies were included, the SRT group included 6 Asian studies with 198

Table 1. Study characteristics (intravenous thrombolysis)

Study [Ref.]	Subjects, n	Period	Country	Design	Mean age ± SD ¹ , years; female gender, n (%)	Stroke severity (NIHSS score)	Additional treatment	Recanalization (TICI 2b–3)	Favorable outcome at 3 months (mRS score 0–2) ¹	Mortality at 3 months ¹	SICH
Huemer et al. [8]	16	1985–1993	Austria	R, S	62±14; 5 (31)	Median 38 ²	0	10 (63%) ³	3 (19%) ⁴	11 (69%)	1 (6%) ^{NS}
Schonewille et al. [9]	121	2002–2007	Europe, USA, Australia, Brazil, Israel	P, M	65±14; 44 (36)	Median 21 (range 12–28)	41× EVT	71 (59%) ⁵	41 (34%) ⁶	41 (34%) ⁶	7 (6%) ^{NS}
Lindsberg et al. [10]	162	1995–2013	Finland	P, S	63±13.7; 49 (30)	Patients with (17±9.9, n = 107) and without (23.2±12, n = 55) recanalization ⁷	Max. 27× EVT	107 (66%) ⁸	55 (34%) ⁹	53 (33%)	16 (10%) ^E
Dias et al. [11]	15	2004–2015	Brazil	R, S	64±14; 7 (47)	Median 28 (IQR 18–36)	0	6 (40%) ¹⁰	3 (20%) ⁹	7 (47%)	0 (0%) ^E
Combined	314	1985–2015	NA	NA	105 (33)	NA	68 (22%)	194 (60%)	102 (31%)	112 (41%)	24 (7%)

R, retrospective; P, prospective; S, single-center; M, multicenter; EVT, endovascular therapy; SICH, symptomatic intracranial hemorrhage; NS, not specified; NIHSS, National Institute of Health Stroke Scale; E, ECASS II criteria; IQR, interquartile range; mRS, modified Rankin Scale; DSA, digital subtraction angiography; TCD, transcranial Doppler; CTA, computed tomography angiography; MRA, magnetic resonance angiography. ¹ If not otherwise specified. ² 12 comatose patients, no further information given, comatose patients were assigned an NIHSS score of 38 [18]. ³ DSA or TCD at different time points. ⁴ Independent of constant support; time point not specified. ⁵ 88% of the patients, at different time points, CTA, MRA, DSA, TCD. ⁶ 1 month. ⁷ Mean ± SD. ⁸ TIMI/TICI 2–3. CTA or MRA at ~24 h. ⁹ mRS score 0–3. ¹⁰ CTA, MRA, DSA, TCD within 7 days.

patients (53%). Most of the studies were retrospective and single-center studies; however, 2 of the 4 IVT studies were prospective. In the SRT group, the Solitaire® and Trevo® devices were most often used. Additional endovascular treatment was performed in 59 cases (16%). In the IVT group, additional treatment was performed in 68 cases (22%). IVT was performed prior to SRT in 128 cases (34%) (Tables 1, 2).

Cumulatively, the target parameters “favorable clinical outcome” (43 vs. 31%, $p = 0.002$) and “successful recanalization” (88 vs. 60%, $p < 0.00001$) were highly significantly more frequently achieved in the SRT group. Mortality was highly significantly lower in the SRT group (22 vs. 41%, $p = 0.0003$). The occurrence of SICH was not statistically significantly different between the two groups (5 vs. 7%, $p = 0.15$) (Fig. 2).

Heterogeneity (I^2) was 18% ($p = 0.301$) for favorable clinical outcome, 37% ($p = 0.190$) for successful recanalization, 69% ($p = 0.021$) for mortality, and 0% ($p = 0.450$) for SICH in the IVT group, while it was 40% ($p = 0.070$), 64% ($p < 0.001$), 58% ($p = 0.004$), and 8% ($p = 0.371$), respectively, in the SRT group.

Discussion

In this meta-analysis, we found a significantly increased recanalization rate, an improved clinical outcome, decreased mortality, and an equal rate of SICH in patients treated with SRT compared to those treated with IVT alone.

Treatment Modality

The results are in line with positive results from recent trials of thrombectomy in the anterior circulation. However, they contradict the results of the BASICS registry [9], which could not demonstrate a superior efficacy of EVT over IVT. Further, a previous meta-analysis could not establish any superiority of either treatment modality [5]. Both studies, however, were performed or included studies before stent retrievers were used. Stent retrievers are currently regarded as the single most effective mechanical thrombectomy device. Technically, they are temporarily deployable stents migrating radially through the thrombus which can subsequently be extracted. They allow for high recanalization rates, as demonstrated in recent trials.

The main criticism of the BASICS registry pertaining to the question of this review is that of the 121 patients included in the IVT group, 41 had received additional EVT. Thus, the effects of the different treatment modalities could not be parsed. In the cohort presented here, 18% (127 of 688) of the patients received 1 additional treatment or 1 additional thrombectomy device was used, and 36% (128 of 374) of the patients treated with SRT had received IVT prior to the intervention. By excluding studies that used >1 thrombectomy device in >50% of the patients, we tried to reduce the effect of combined therapies.

Clinical Outcome

As the most important result, we found a higher rate of favorable outcomes as well as decreased mortality after SRT. An mRS score ≤ 2 at 90 days is considered to represent functional independency and thus a favorable outcome. Although this threshold has not been validated and some authorities have questioned the adequacy of using this threshold for BAO [10, 11], we chose to adhere to this strict definition of favorable outcome. Had we chosen a less strict definition of favorable outcome, the result in favor of SRT would probably have been even more pronounced. Further, some patients ($n = 152$) were followed up at other time points.

Table 2. Study characteristics (stent retriever thrombectomy)

Study [Ref.]	Subjects, n	Period	Country	Design	Mean age ± SD ¹ , years; female gender, n (%)	Device	Stroke severity (NIHSS score)	Additional EVT	IVT	Recanalization (TICI 2b–3) ¹	Favorable outcome at 3 months (mRS score 0–2) ¹	Mortality at 3 months ¹	SICH
Costalat et al. [12]	16	2009–2010	France	P, S	NA	Solitaire	?	0	10 (62%)	13 (81%) ²	7 (44%)	4 (25%)	NA
Espinosa de Rueda et al. [13]	18	2010–2012	Spain	R, S	Median 67.5 (range 32–87); 5× Trevo 11 (61)	13× Solitaire Mean 20.4 ³	Mean 20.4 ³	0	0 (0%)	17 (94%)	9 (50%)	4 (22%)	NA
Lefevre et al. [14]	25	2010–2012	France	R, S	NA	Solitaire	Mean 19.9	9× rtPA	1 (4%)	23 (92%)	14 (56%)	10 (40%)	NA
Mourand et al. [15]	31	2009–2011	France	R, S	61±17; 16 (52)	Solitaire	Median 38 (range 9–38) ⁴	0	19 (61%)	23 (74%)	11 (35%) ⁵	10 (32%)	5 (16%) ^E
Möhlenbruch et al. [16]	24	2009–2012	Germany	R, S	Median 70 (range 33–83); 7 (29)	12× Revive 2× both	Median 24 (range 7–42)	6× rtPA	21 (88%)	18 (75%)	8 (33%)	7 (29%)	1 (4%) ^{PII}
Baek et al. [17]	25	2010–2012	South Korea	P, S	68; 11 (44)	Solitaire	Mean 11	3× Penumbra 1× urokinase	6 (24%)	24 (96%)	12 (48%)	3 (12%)	0 (0%) ^F
Carneiro et al. [18]	24	2012–2014	Portugal	R, S	57 (range 27–80); 7 (29)	21× Trevo 3× Solitaire	Median 20 (range 12–36)	0	11 (46%)	15 (63%)	5 (21%)	8 (33%)	0 (0%) ^F
Wang et al. [19]	18	2011–2013	China	R, S	59.56±10.35; 6 (33)	Solitaire	Median 25.5 (range 20–35) ⁶	8× IA rtPA	NA	17 (94%)	7 (39%)	5 (28%)	1×SAH (6%) ^{NS}
Yoon et al. [20]	50	2010–2015	South Korea	R, S	71 (range 63–77); 24 (48)	Solitaire and Trevo	Median 10.5 (IQR 7.75–16)	6× Penumbra 2× urokinase	14 (28%)	48 (96%)	27 (54%)	6 (12%)	0 (0%) ^{NS}
Gory et al. [21]	22	2010–2014	France	R, S	Median 60 (range 31–76); 8 (36)	Solitaire	Mean 13.6 (range 4–22, n = 12) ⁷	2× rtPA	8 (36%)	16 (73%)	6 (27%)	10 (46%)	3 (14%) ^{B@24h}

Table 2 (continued)

Study [Ref.]	Subjects, n	Period	Country	Design	Mean age ± SD ¹ , years; female gender, n (%)	Device	Stroke severity (NIHSS score)	Additional EVT	IVT	Recanalization (TICI 2b–3) ¹	Favorable outcome at 3 months (mRS score 0–2) ¹	Mortality at 3 months ¹	SICH
Lee et al. [22]	62	2010–2016	South Korea	R, S	69.6±11.95 (range 31–76); 26 (42)	Solitaire	Mean (SD) 12.4±6.23	11× manual aspiration	17 (27%)	60 (97%)	33 (53%)	10 (16%)	1 (2%) ^E
Wen et al. [23]	19	2013–2015	China	R, S	Median 62 (IQR 56–75); 3 (36)	16× Solitaire; 3× Revive	Median 26 (IQR 14–35)	4× stenting	5 (26%)	17 (89%)	10 (53%)	1 (5%)	NA
Hu et al. [24]	24	2013–2016	South Korea	R, S	Median 65.7 (IQR 32–85); 11 (46)	14× Solitaire; 10× Trevo	Mean 14.2 (IQR 2–34)	0	9 (38%)	19 (79%)	10 (42%)	4 (17%)	1 (4%) ^{NS}
Combined	358	2008–2016	NA	NA	139 (38)	NA	NA	59 (16%)	128 (36%)	310 (88%)	159 (43%)	82 (22%)	12 (5%)

R, retrospective; P, prospective; S, single-center; M, multicenter; EVT, endovascular therapy; IVT, intravenous thrombolysis; SICH, symptomatic intracranial hemorrhage; SAH, subarachnoid hemorrhage; rtPA, recombinant tissue plasminogen activator; NA, not applicable; NS, not specified; NIHSS, National Institute of Health Stroke Scale; E, ECASS II criteria; E@24h, ECASS II criteria at 24 h; PII, PROACT II criteria. ¹If not otherwise specified. ²TICI 3. ³Baseline NIHSS score not given for intubated patients (n = 4). ⁴Maximum prethrombectomy NIHSS score. ⁵Median 240 days. ⁶Median NIHSS score calculated by individual patient data given in the manuscript. ⁷10 comatose patients; comatose patients were assigned an NIHSS score of 38 [18].

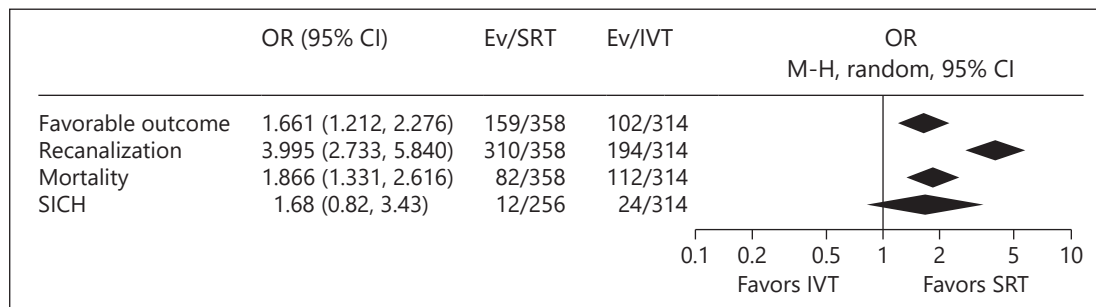


Fig. 2. Detailed results with forest plots. OR, odds ratio; CI, confidence interval; Ev, events; SRT, stent retriever thrombectomy; IVT, intravenous thrombolysis; SICH, symptomatic intracranial hemorrhage; M-H, Mantel-Haenszel.

Recanalization

We found a significantly higher recanalization rate among patients treated with SRT. This finding is not new, as a previous meta-analysis had demonstrated higher recanalization rates with EVT in general than with IVT. The success of recanalization with IVT was demonstrated to be dependent on thrombus length. Long thrombi were shown to be more resistant both in the anterior [25] and the posterior circulation [26]. In contrast, it was recently demonstrated that EVT is effective even when dealing with long thrombi [27, 28].

In patients treated with SRT, BAO was proven directly prior to therapy via the gold standard digital subtraction angiography. In contrast, many patients receiving IVT were diagnosed by magnetic resonance angiography, with the caveat of possible overestimation of a stenosis and misclassification as an occlusion. Conversely, demonstration of vessel patency in patients treated with SRT was immediately available. In contrast, patients treated with IVT were observed within undefined time spans after therapy by various imaging modalities.

It is often stated that imaging parameters should be used to select patients eligible for therapy. In summary, patients with extensive infarctions in the brain stem and the posterior territory are less likely to benefit from recanalization. Various techniques ranging from nonenhanced cranial computed tomography (CT) [29], CT angiography source imaging [30], and CT perfusion [31] to diffusion-weighted magnetic resonance imaging [32] have been used to identify infarcted tissue. However, recanalization itself has been identified as a condition without which only a minimal chance of favorable outcome is reported [5, 10].

Symptomatic Intracranial Hemorrhage

We found an equal rate of SICH in the two treatment groups. The overall rate of occurrence of SICH was low, so these results certainly have to be regarded with caution. In most of the studies, SICH was defined according to the ECASS II criteria. Various other definitions have been used, especially in the era preceding the ECASS. The incidence of SICH found here is in the order of magnitude of the incidence of SICH in IVT trials [33] and recent thrombectomy trials [6, 7].

There are several limitations to our results. The data presented here cannot replace a randomized controlled trial. Only a minority of the studies were designed prospectively, and none directly compared IVT and SRT. This introduces several possibilities for bias, especially heterogeneity in the baseline characteristics of the included subjects. Since data on baseline characteristics were either not given (e.g. medication), incomplete (missing data), or inconsistent (different measures of location), they are listed in Tables 1 and 2, but no reliable statistical comparison could be made. In the absence of controlled trials, it has to be stressed that heterogeneity in baseline characteristics is expected to be large.

Furthermore, data on IVT only for BAO are limited, and few studies contribute the bulk of the patient cohort. Studies on the IVT cohort date back as far as 1985, which can be regarded as “historical.” Although the majority of patients were included after 1995, an influence of major achievements in stroke medicine – such as greater availability of stroke units and changes in medical therapy such as statin use and dual platelet inhibition – on overall outcome cannot be excluded. Especially older studies did not report outcome parameters using scales which are in use today (the NIHSS for clinical symptoms at admission, the ECASS criteria for intracranial hemorrhage, and the mRS for functional outcome) and thus do not provide standardized, comparable results.

We provide comprehensive data on a comparison between IVT and latest-generation SRT. Previous meta-analyses have focused primarily on outcome parameters alone [34], compared intraarterial thrombolysis with mechanical thrombectomy [35], focused solely on SRT [21, 36], or compared IVT with EVT including intraarterial pharmacological thrombolysis and mechanical thrombectomy including first-generation devices or omitted older work [5, 10].

The results of randomized controlled trials currently conducted [37] are expected to shed light on this question still unanswered in stroke medicine. Recently, the results of the BEST trial (NCT 02441556) have been published as a conference abstract [38]. The BEST trial was designed as a multicenter prospective randomized controlled trial in China. The trial was terminated prematurely because of high crossover rates between the treatment groups. In conclusion, no superiority of thrombectomy over medical treatment could be demonstrated in the intention-to-treat analysis. However, the patients eventually treated with EVT fared better than the patients treated medically alone.

In conclusion, the data from this meta-analysis suggest a possible superiority of SRT over IVT, pending positive results of randomized controlled trials. Our results support the approach suggested by several international organizations [39]: if no contraindications exist, patients with acute BAO should receive IVT and be transferred to a neurovascular center, where mechanical thrombectomy preferably with stent retrievers can be performed.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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