Therapy of Basilar Artery Occlusion
A Systematic Analysis Comparing Intra-Arterial and Intravenous Thrombolysis

Perttu J. Lindsberg, MD; Heinrich P. Mattle, MD

Background and Purpose—Basilar artery occlusion (BAO) is an infrequent form of acute stroke, which invariably leads to death or long-term disability if not recanalized. A traditional recanalization approach based on historical controls and pathophysiological consideration is local intra-arterial thrombolysis (IAT) in eligible patients. This necessitates diagnostic evaluation and treatment in stroke centers equipped with an interventional neuroradiological service on a 24-hour basis, but its superiority to the technically simple intravenous thrombolysis (IVT) remains unproven.

Methods—We analyzed systematically published case series of substantial size reporting the outcome of BAO after IAT or IVT.

Results—In 420 BAO patients treated with IVT (76) and IAT (344), death or dependency were equally common: 78% (59 of 76) and 76% (260 of 344), respectively (P = 0.82). Recanalization was achieved more frequently with IAT (225 of 344; 65%) than with IVT (40 of 76; 53%; P = 0.05), but survival rates after IVT (38 of 76; 50%) and IAT (154 of 344; 45%) were equal (P = 0.48). A total of 24% of patients treated with IAT and 22% treated with IVT reached good outcomes (P = 0.82). Without recanalization, the likelihood of good outcome was close to nil (2%).

Conclusions—Recanalization occurs in more than half of BAO patients treated with IAT or IVT, and 45% to 55% of survivors regain functional independence. Although improved therapy forms for BAO are necessary, hospitals not equipped for IAT may set up IVT protocols. The effect of IVT is probably not much different from the effect of IAT. IVT represents probably the best treatment that can be offered to victims of acute BAO in such hospitals. (Stroke. 2006; 37:922-928.)

Key Words: basilar artery ■ brainstem stroke ■ posterior circulation brain infarction ■ stroke management ■ thrombolysis

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proximately one fifth of ischemic strokes occur in the posterior circulation supplied by vertebrobasilar arteries, where basilar artery occlusion (BAO) tends to cause the most desolate strokes. Ischemic damage to the pontine pyramidal tracts creates the devastating locked-in syndrome characterized by quadriplegia, anarthria, and preserved consciousness.1 Extended infarctions in this territory also carry a tall acute death toll attributable to destruction of cranial nerve nuclei and centers for vasomotor and respiratory regulation in the midbrain, pons, and medulla. Dominant etiologic factors such as local thrombosis or artery-to-artery thromboembolism originating from arteriosclerotic lesions account for >50% of BAOs.2,3 Other major etiologies are cardiac emboli and vertebral artery dissections. Fatality rates without treatment are up to 90%, and the chances for independent outcomes are negligible.4,5 Such a gloomy prognosis stands in contrast to the natural course of most other stroke types. Only stroke after carotid T occlusion in the anterior circulation tends to be as devastating as stroke after BAO.

BAO has been divided into 3 major clinical types of presentations characterized by different modes of symptom onset:2,6 (1) sudden onset of severe motor and bulbar symptoms such as quadriplegia, ophthalmoplegia, and anarthria combined with reduced consciousness; and (2) gradual or stuttering course of posterior circulation symptoms such as blurred vision, balance disturbance, dysarthria, bilateral parasthesiae, or motor weakness, which finally become disabling and reduce consciousness. The former presentation is more often cardioembolic in origin and the second more often atherothrombotic. Embolic occlusions of the BA are often distal,7,8 whereas atherothrombotic occlusions affect more frequently the proximal or middle segments of the BA.2,3,7 A third clinical type of presentation is characterized by transient prodromal symptoms (double vision, dysarthria, vertigo, parasthesiae), which precede the monophasic BAO symptoms by several days or even months.2 Such prodromal symptoms occur in >60% of patients who eventually develop BAO. They mostly represent isolated transient ischemic attacks2,5

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and highlight the need for immediate vascular evaluation and therapeutic intervention.

The differential diagnosis of BAO to other major central nervous system catastrophes is often difficult and depends on a wide repertoire of ancillary and imaging methods. Therefore, by far, the most rapid and cost-effective approach is to evaluate the vessels outright with magnetic resonance angiography (MRA), computed tomography (CT) angiography (CTA), intra-arterial digital subtraction angiography (DSA), or in experienced hands ultrasound. With the advent of spiral CT, CT examination can be combined with CTA and has become a reliable and fast diagnostic procedure. A more traditional diagnostic approach involves DSA, which has the therapeutic advantage to deliver thrombolytics in situ whenever a treatable occlusion is detected. Analyses of the cost-effectiveness and let alone of the therapeutic results based on these 2 diagnostic approaches are not available but would be of crucial importance in establishing standard protocols for thrombolysis of BAO.

The immediate therapy uses antithrombotic and thrombolytic agents. Their choices depend on the nature and severity of the leading symptoms, and their goal is to halt the progression of BAO or even reverse it. Because BAO is rare and its clinical presentation variable, evidence-based data on the magnitude of benefit of thrombolytic recanalization compared with anticoagulants are scarce.4 Based on a number of mainly small-sized case series and a few larger thrombolysis cohorts, numerous stroke centers have adopted standing protocols to reverse BAO. Most use intra-arterial thrombolysis (IAT), which has accumulated the most abundant outcome data.4,5,9–14 Instead of witnessing the natural course of BAO, regardless of uncertain efficacy data, the current therapy recommendation is to strive for recanalization with thrombolytics.5,15,16 Therapy guidelines in different hospitals vary a great deal with respect to the intra-arterial (endovascular, local) versus intravenous (systemic) therapy modes, time window for eligibility, and choice of thrombolytic drug. There are protocols that limit thrombolysis only to acute cases (<12 hours after symptom onset)9,13,17 and those with considerably more extended time windows, up to 2 or 3 days in selected cases.9,8,14,19,20 The only randomized trial to compare IAT with urokinase versus anticoagulants in stroke attributable to posterior circulation arterial occlusion (Australian Urokinase Stroke Trial) was halted because urokinase was withdrawn from the Australian market after 16 patients had been included. It showed a nonsignificant trend toward favorable outcomes in the IAT group (4 of 8 favorable outcomes) compared with anticoagulants (1 of 8 favorable outcomes).21

Because of insufficient data from the 2 alternative therapy modes IAT and intravenous thrombolysis (IVT), the preferential route of thrombolytic administration has so far not been determined. Lack of well-balanced comparison of literature-based outcome descriptions or a large randomized trial has led to various views on the preferred therapy that are not based on comparative evidence.22 Systemic thrombolysis has been linked with less frequent recanalization and more frequent hemorrhagic complications,15 the latter having been recently supported by experiments in an animal model.23 However, both IVT and endovascular recanalization techniques have advantages and disadvantages. IVT can be applied without delay after diagnosis of BAO and may help reflow both in the BA and at the capillary level. Arteriography, on the other hand, for endovascular recanalization techniques needs time during which additional neurons potentially die. However, when mechanical recanalization succeeds, the vessel is reopened after a few minutes, much faster than with the average pharmacological recanalization.

Last year, 2 relatively large-sized cohorts of consecutive patients were published.13,14 This prompted us to perform a systematic review that may assist hospitals in making evidence-based guidelines for acute BAO therapy.

Material and Methods

Criteria for Selecting Studies for the Systematic Review

We identified studies that included consecutive patients who had been treated with IAT or IVT using various substances to reverse acute BAO. The publication of the study had to be in a peer-reviewed international scientific journal. To minimize the influence of chance and anecdotal patient outcomes, the analysis was limited to case series of ≥10 patients. Cohorts based on a major portion of distal vertebral artery occlusions were not included because these tend to have a more benign natural course than BAO.2,3 Studies lacking angiographic evidence of BAO or studies without explicit functional outcome data were excluded as well. Studies had to report BAO as an ad hoc acute clinical emergency with regard to symptom duration; retroactive evaluations with radiographic registry data as the entry criteria were thus not included.

Data Collection

Because of the considerable variability of clinical presentation, we paid special attention to the timing of therapy and the clinical condition before treatment. The timing of therapy was scrutinized case by case from the symptom-to-thrombolysis times. This enabled us to weigh the case mix in the ultra-acute window (within 6 hour) and acute window (within 12 hours), which could have paramount importance in the time-dependent loss of ischemic cerebral tissue. The baseline neurologic condition on admission was recorded as the percentage of comatose patients (Glasgow Coma Scale ≤8 of 15 if provided). Furthermore, we noted the diagnostic angiographic method and whether the treatment protocol included heparin in addition to thrombolytic agents.

Four types of outcome data could be collected systematically: (1) the rate of survival; (2) the rate of recanalization, complete or partial (corresponding to Thrombolysis in Myocardial Infarction [TIMI] 3 or 2) versus nil or minimal (TIMI 0 or 1); (3) the rate of cerebral hemorrhagic complications such as symptomatic hemorrhages or parenchymal hematomas; and finally (4) the rate of good or favorable outcome was recorded as provided in the reports. If individual patient data were provided, we considered Rankin scores 0 to 2, Barthel index 95 to 100, or Glasgow Outcome Scale 5 as good outcomes. The time of scoring the functional outcomes varied from study to study. Therefore, outcome scores approximating a 3-month outcome were used if provided. All included reports and collected data are listed in Table 1.

Statistics

Odds ratio (OR) analysis for the combined data sets was performed using Mantel–Haenszel risk ratio estimation for the individual clinical end points. χ² test was also used to determine the statistical significance of differences in outcome events in the 2 therapeutic approaches.
<table>
<thead>
<tr>
<th>Study (n)</th>
<th>Female/ Male Mean Age, y</th>
<th>MRA Route</th>
<th>Drug</th>
<th>Window (h) Mix ≤12 h &gt;12 h ≤6 h &gt;6 h</th>
<th>Comatose on Admission n, %</th>
<th>Recanalized n, %</th>
<th>Symptomatic Hemorrhage/ Parenchymal Hematoma n, %</th>
<th>Survival n, %</th>
<th>Good Outcome n, % Time evaluated</th>
<th>Definition of Good Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hennerici 1991 (10)</td>
<td>7/3</td>
<td>55</td>
<td>DSA</td>
<td>IV Alteplase</td>
<td>&lt;24 h, mix NA</td>
<td>4/10, 40</td>
<td>4/10, 40</td>
<td>0/10, 0</td>
<td>3/10, 30</td>
<td>2/10, 20</td>
</tr>
<tr>
<td>Huemer 1995 (16)</td>
<td>5/11</td>
<td>62</td>
<td>DSA</td>
<td>IV Alteplase</td>
<td>&lt;7 h 16:0 100%:0% 13:3 18%:91%</td>
<td>12/16, 75</td>
<td>10/16, 63</td>
<td>1/16, 6</td>
<td>5/16, 31</td>
<td>3/16, 19</td>
</tr>
<tr>
<td>Lindsberg 2004 (50)</td>
<td>13/37</td>
<td>62</td>
<td>MRA/DSA</td>
<td>IV Alteplase</td>
<td>&lt;48 h 35:15 70%:30% 6:44 12%:88%</td>
<td>23/50, 46</td>
<td>26/50, 52</td>
<td>7/50, 14</td>
<td>30/50, 60</td>
<td>12/50, 24</td>
</tr>
<tr>
<td>Combined IVT (76)</td>
<td>25/51</td>
<td>33%/67%</td>
<td>DSA/DSA</td>
<td>IV Alteplase</td>
<td>51:15 77%:23% 19:47 29%:71%</td>
<td>39/76, 51</td>
<td>40/76, 53</td>
<td>8/76, 11</td>
<td>38/76, 50</td>
<td>17/76, 22</td>
</tr>
<tr>
<td>Hacke 1988** (43)</td>
<td>15/28</td>
<td>52</td>
<td>DSA</td>
<td>IA Urokinase Streptokinase</td>
<td>&lt;24 h 6:37 (&lt;6 h:&gt;) 14%:86%</td>
<td>11/43, 26</td>
<td>19/43, 44</td>
<td>4/43, 9</td>
<td>13/43, 30</td>
<td>10/43, 23</td>
</tr>
<tr>
<td>Brandt 1996 (51)</td>
<td>19/32</td>
<td>55</td>
<td>DSA</td>
<td>IA (6 IV) Urokinase Alteplase</td>
<td>&lt;48 h mix NA</td>
<td>26/51, 51</td>
<td>26/51, 51</td>
<td>3/51, 6</td>
<td>16/51, 31</td>
<td>10/51, 20</td>
</tr>
<tr>
<td>Cross 1997** (20)</td>
<td>NA</td>
<td>57</td>
<td>DSA</td>
<td>IA Urokinase</td>
<td>&lt;79 h 9:11 45%:55% 3:17 15%:85%</td>
<td>11/20, 55</td>
<td>12/20, 60</td>
<td>5/20, 25</td>
<td>7/20, 35</td>
<td>4/20, 20</td>
</tr>
<tr>
<td>Levy 1999 (10)</td>
<td>8/2</td>
<td>50</td>
<td>DSA</td>
<td>IA Urokinase</td>
<td>&lt;22 h 7:3, 70%:30% 0:10 0%:100%</td>
<td>8/10, 80</td>
<td>10/10, 100</td>
<td>NA</td>
<td>3/10, 30</td>
<td>2/10, 20</td>
</tr>
<tr>
<td>Egan 1999 (15)</td>
<td>7/8</td>
<td>59</td>
<td>DSA</td>
<td>IA Urokinase</td>
<td>&lt;48 h 12:3 80%:20% 5:10 33%:77%</td>
<td>NA</td>
<td>12/15, 80</td>
<td>1/15, 7</td>
<td>10/15, 67</td>
<td>4/15, 27</td>
</tr>
<tr>
<td>Berg-Dammer 2000 (20)</td>
<td>7/13</td>
<td>56</td>
<td>DSA</td>
<td>IA Streptokinase/ urokinase</td>
<td>&lt;48 h 3:17 (&lt;12 h:&gt;) 15%:85%</td>
<td>6/20, 30</td>
<td>16/20, 80</td>
<td>0/20, 0</td>
<td>13/20, 65</td>
<td>8/20, 40</td>
</tr>
<tr>
<td>Slivka 2001 (36)</td>
<td>8/28</td>
<td>58</td>
<td>DSA</td>
<td>IA Urokinase/ alteplase</td>
<td>&lt;36 h 23:13 (&lt;6 h:&gt;) 64%:36% severe deficits</td>
<td>21/36, 58</td>
<td>20/36, 56</td>
<td>3/36, 8</td>
<td>17/36, 47</td>
<td>6/36, 17</td>
</tr>
<tr>
<td>Eckert 2002**#§ (83)</td>
<td>19/64</td>
<td>60</td>
<td>DSA</td>
<td>IA Urokinase Alteplase/ lysplasminogen</td>
<td>&lt;18 h (76 known) 60:16 79%:21% 33:43 43%:57%</td>
<td>NA</td>
<td>54/83, 66</td>
<td>7/83, 8</td>
<td>33/83, 40</td>
<td>19/83, 23</td>
</tr>
<tr>
<td>Ezaki 2003§ (26)</td>
<td>7/19</td>
<td>67</td>
<td>DSA</td>
<td>IA Alteplase/ urokinase/ prourokinase</td>
<td>&lt;12 h 26:0 100%:0% 13:13 50%:50%</td>
<td>NA</td>
<td>24/26, 92</td>
<td>2/26, 8</td>
<td>19/26, 73</td>
<td>7/26, 27</td>
</tr>
</tbody>
</table>

(Continued)
**Results**

**Study Characteristics**

The literature search yielded data from 76 patients in 3 studies of IVT and 344 patients in 10 studies of IAT. The intra-arterial studies used preferentially urokinase, whereas all intravenous protocols used alteplase like in anterior circulation stroke trials. All patients treated intravenously had heparin as an adjuvant antithrombotic therapy, which is comparable to the 81% rate of heparin use in the intra-arterial studies. All patients with IAT had the diagnosis made with DSA, whereas various methods (DSA, MRA) were used in the IVT protocols.

**Baseline Parameters**

To study the homogeneity of case mix with regard to prognostically important baseline characteristics, we recorded the percentages of patients who received thrombolysis within ultra-acute (<6 hours of symptom onset) and acute (<12 hours) time windows as well as the percentages of patients who were comatose before treatment. There was a nonsignificant trend that more intravenously treated patients had missed the ultra-acute therapy window (29% versus 42% in the intra-arterial protocols \( P = 0.066 \)). The number of comatose patients at baseline did not differ (51% versus 45%; \( P = 0.37 \); Figure 1).

**Outcome**

The rates of death or dependency were 77.6% (59 of 76) in the IVT patients and 75.6% (260 of 344) in the IAT patients. The difference of 2.0% favoring IAT was not significant (\( \chi^2 \) test; \( P = 0.82 \); OR, 1.04; 95% CI, 0.72, 1.53; Figure 2). The survival rates were 50% (38 of 76) after IVT and 50% (170 of 344) after IAT.

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**TABLE 1. (Continued)**

<table>
<thead>
<tr>
<th>Study (n)</th>
<th>Female/Male</th>
<th>Age, y</th>
<th>MRA</th>
<th>Route</th>
<th>Drug</th>
<th>Window (h) Mix</th>
<th>Comatose on Admission</th>
<th>Recanalized</th>
<th>Symptomatic Hemorrhage/Parenchymal Hematoma</th>
<th>Survival</th>
<th>Good Outcome</th>
<th>Definition of Good Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnold 2004 (40)</td>
<td>18/22</td>
<td>58</td>
<td>DSA</td>
<td>IA</td>
<td>Urokinase</td>
<td>&lt;12 h</td>
<td>15/40, 38</td>
<td>24/40, 50</td>
<td>2/40, 5</td>
<td>23/40, 58</td>
<td>14/40, 35</td>
<td>Favorable</td>
</tr>
<tr>
<td>Combined IAT (344)</td>
<td>108/216</td>
<td>33%</td>
<td>DSA</td>
<td>IA</td>
<td>Several</td>
<td>&lt;12 h</td>
<td>157/50</td>
<td>98/220, 45</td>
<td>225/344, 65</td>
<td>27/334, 8</td>
<td>154/344, 45</td>
<td>84/344, 24</td>
</tr>
</tbody>
</table>

**Notes:**

**Studies include also minor population of bilateral vertebral occlusions. Studies with predominantly vertebral bilateral occlusions (Becker et al, 1996) or nonangiographic diagnosis (Grond et al, 1998) have been excluded.


§Study included occasional patients treated also with percutaneous transluminal angioplasty (PTA).

Individual data provided in the publication were applied to obtain fraction of patients with no to mild neurological deficit (NIHSS ≤5), equaling 0 to 2 in modified Rankin Scale (mRS).

NIHSS indicates National Institutes of Health Stroke Scale.

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**Figure 1.** Case mix of baseline variables. The first 2 pairs of bars compare the case mix of IVT and IAT studies with regard to the onset of treatment arranged by 2 different time windows: 6 hours and 10 to 12 hours. The third bar pair illustrates the case mix of clinical condition of the patients on admission with regard to the presence or absence of coma. All differences in these baseline variables were statistically nonsignificant. Data were analyzed only to the extent they were available in the published reports, as listed in Table 1. Data regarding other baseline variables such as vascular cause of the BAO, type of clinical onset, and risk factors were not provided as frequently in the included reports as would be necessary for systematic presentation.

**Figure 2.** The ORs and 95% CIs for death, dependence, and death/dependence. Statistical data are based on calculating the Mantel-Haenszel ORs separately for the individual group data.
Discussion

It has been shown previously that outcome of acute BAO depends on the clinical state at presentation, the length and location of the occlusion, the degree of recanalization, and the time to treatment.9,11–13,17,18,24 This systematic review adds to our knowledge on prognosis of BAO that once the decision to give thrombolysis has been made, their route of administration does not play a major role for clinical prognosis. This finding has important implications for the routine management of most patients with BAO.

Patients treated with IVT and IAT had equal odds of death or dependency: 78% after IVT and 76% after IAT (P = 0.82). However, these results may have been biased by some imbalances in the baseline variables of IVT and IAT patients. For instance, there was a trend that IVT patients were treated later (P = 0.066) and were in a slightly poorer clinical state (Figure 1), although none of the case-mix factors that could be analyzed reached significance. Radiographic evidence of brain stem infarction was stated as an exclusion criterion in several large intra-arterially treated cohorts9,12,25 but not in the largest IVT series.14 This may have created an imbalance favoring good outcomes reported in IAT series. Nevertheless, the outcome neither after IVT nor IAT is a reason for satisfaction. Death rates of 50% and 55% and dependency rates of 28% and 21% clearly show that major therapeutic advances in BAO are needed.

Recanalization of BAO is the immediate therapeutic goal of thrombolysis. If recanalization cannot be achieved, there are hardly any chances of good outcome (2%), but when at least some patency of basilar artery can be reached, the odds of a favorable outcome rise substantially (38%; Table 2). Recanalization was noted more frequently after IAT (65%) than after IVT (53%; P = 0.05), but this surprisingly did not influence the outcome of the 2 groups. However, different vascular diagnostic procedures may hinder reliable comparison of the recanalization rates between IVT and IAT. Survival and dependency rates were equal after IVT and IAT. Rather than depending on the route of administration of thrombolytics, the rates of recanalization are influenced by the occluded segment of the basilar artery; the distal, typically embolic occlusions7,8 recanalize more easily than the more proximal ones9,11–13,18,24. In addition, 2 recent studies suggest that recanalization is also more likely if thrombolysis can be started early.12,13

Hemorrhagic complications were slightly but not significantly more frequent after IVT (11%) than after IAT (8%; P = 0.59). This indicates that the gross hemorrhage risk of systemic thrombolysis obtained in animal models was not reproduced in humans.23 Furthermore, the symptomatic hemorrhages after IVT was observed only after failed recanalization in patients destined to poor prognosis.14 On the other hand, periprocedural complications with IAT may have been underreported because the exact cause of bleeding remains mostly unknown.18,26 Overall, the risk of symptomatic hemorrhages of 8% to 11% after IAT and IVT for BAO is similar to the bleeding risk of thrombolysis for anterior circulation strokes.27 However, unequivocal factors advising against thrombolysis in BAO because of enhanced bleeding risk in a given patient are not known.

The studies established BAO diagnosis mainly with DSA and occasionally with MRA. As noted,15 the advent of DSA as a screening instrument may expedite the initiation of IVT, which tended to be less urgently administered than IAT (Figure 1). Patients treated with IVT had the initial CT followed by MRA or DSA, which may explain the delayed start of thrombolysis. Stroke centers that establish standard protocols using CTA as a sole diagnostic tool before IVT may report improved rates of recanalization and functional outcome in the future. On the other hand, because residual stenoses and reclosures are common problems, similar advances may be achieved by more effective endovascular

Table 2. Likelihood of Good Functional Outcome With Respect to the Recanalization State (complete or partial)

<table>
<thead>
<tr>
<th>Recanalization State</th>
<th>Good Outcome</th>
<th>Poor Outcome</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recanalization +</td>
<td>94 (38%)</td>
<td>151 (62%)</td>
<td>245</td>
</tr>
<tr>
<td>Recanalization −</td>
<td>3 (2%)</td>
<td>136 (98%)</td>
<td>139</td>
</tr>
</tbody>
</table>

The rates of good and poor outcome were highly significantly different in patients with and without recanalization (Fisher exact test P < 0.001). Data were derived from all listed studies except for the study by Slivka, from which the analysis could not be derived. The data were similar in IVT and IAT (Hacke et al, 1998; Hennerici et al, 1991; Huemer et al, 1995; Brandt et al, 1996; Cross et al, 1997; Levy et al, 1999; Egan et al, 1999; Berg-Dammer et al, 2000; Eckert et al, 2002; Ezaki et al, 2003; Lindsberg et al, 2004; Arnold et al, 2004).
devices for clot aspiration or local dissolution and combinations of thrombolysis with percutaneous transluminal angioplasty or stenting.\textsuperscript{12,28–32} Platelet deaggregants such as glycoprotein IIb/IIIa antagonists, as known from case series, are also valuable treatment adjuncts especially in patients with residual stenosis and risk of reocclusion.

Recent studies have indicated that the successful thrombolytic reversal of BAO depends on the early initiation of treatment.\textsuperscript{12,13} but contrasting evidence also exists.\textsuperscript{9,18,24,25} The degree of collateral circulation has also been found to influence the neurologic outcome.\textsuperscript{33} It is possible that differences in the case mix among the 3 clinical presentation types have influenced the differences in the results of these individual case series. If mainly patients with early onset of massive symptoms are treated, the chances of meaningful recovery may be more time dependent than in studies that include also patients with progressive, or waxing and waning symptoms. BAO is an entity within ischemic stroke in which salvageable tissue exists well beyond the time window for anterior circulation stroke thrombolysis (≤3 hours), possibly because of slower progression of ischemic tissue damage.\textsuperscript{26} Clearly, the decision to resort to thrombolysis should depend on characterizing the underlying vascular lesion rather than time only,\textsuperscript{34} which can also be supported by rapid mapping of perfusion mismatch indicative of salvageable tissue.\textsuperscript{26} However, long duration of coma as such probably has a negative predictive value.\textsuperscript{4,9,13}

As expected, a limitation of the present study was that the reports used different functional scales to indicate favorable outcome, a few stating it only in vague terms such as “minimal or moderate deficit”\textsuperscript{4} or “good outcome.”\textsuperscript{35} In reports that listed all patient outcomes individually, we defined modified Rankin index 0 to 2, Barthel index of 95 to 100, National Institutes of Health Stroke Scale of 0 to 5 or good recovery on Glasgow Outcome Scale to best approximate good outcome but were unable to guarantee coherence for reports without explicit scoring. There was also heterogeneity in the timing of assessing the functional outcome, some reporting outcome on discharge or after several years. Fortunately, most of the more recent reports with the largest number of patients used relatively uniform scales performed at 3 months. Furthermore, some reports compared the long-term functional outcome\textsuperscript{14,20} and vessel patency\textsuperscript{24} with the situation at intermediate follow-up or 3 months and found them very consistent.

Another potential source of inaccuracy was the variability in the clinical syndromes, but we demonstrated good coherence in the treatment time window and clinical severity within the 2 compared thrombolytic approaches (Figure 1). It was beyond the scope of the present analysis to examine the strength of previously reported prognostic baseline variables such as therapy timing, etiology, or length and location of BAO. The drug dose may be another potential weakness of this analysis. In the intravenous series, the recombinant tissue plasminogen activator dose is rather uniform. However, in the intra-arterial series, the dose of the administered medication varied considerably. We should also note that because the IVT studies accounted for <20% of the total number of patients within the analyzed studies, there may be imbalance between the compared series in terms of covering the full spectrum of disease phenotypes included in the 2 protocols. Furthermore, because 50 of the 76 patients treated with IVT were from a single center,\textsuperscript{14} we would recommend other centers to report their results to add to the reliability of the comparison.

That IAT is not superior to IVT is somewhat surprising. In the earliest IAT studies, there were only a few subjects treated within 6 hours, and therefore few patients may have had chances of survival and of good functional outcome despite favorable vascular outcomes. Time lost until the decision to treat and during selective catheterization may have accounted for this. Furthermore, the significance of local delivery of thrombolytics to achieve high local drug concentrations may have been overestimated. On the other hand, recent cohorts with mechanical clot disruption are generally small and were not included in our analysis, although such techniques combined with thrombolytics may improve the outcome. Furthermore, because BAO often evolves on vertebrobasilar occlusive disease, which contributes to the often undulating course and frequent recurrences, there is certainly a need for endovascular techniques to reopen the occluded BA and to keep it patent, either alone or in conjunction with pharmacological means. The heterogeneous phenotypes and the high prevalence of stenoses underlying basilar occlusive disease clearly call for novel endovascular techniques that can be used on an individual basis.\textsuperscript{28–32}

From our analysis, 2 main conclusions can be drawn. The currently available data indicate that the route of drug delivery for treatment of BAO does not make a difference in clinical outcome. The chances of recanalization, which can almost be regarded as a condition \textit{sine qua non} for a favorable outcome (Table 2), is slightly higher after IAT compared with IVT. Therefore, centers that have an interventional neuroradiology service should pursue IAT to treat their patients with BAO. However, there is no reason for stroke centers with diagnostic equipment such as MRA or CTA but without an interventional neuroradiologist to refrain from thrombolysis. Current data indicate that the odds for survival without a handicap improve equally after IVT and IAT. The data from this analysis encourage such hospitals to use IVT for treatment of patients with BAO. This would make thrombolysis available for many more patients and increase the likelihood to survive with meaningful outcome after this devastating disease. Because treatment delay is unnecessary and harms the patient, there should be no reason to delay any form of available recanalization therapy. Based on the nearly equal efficacy of IVT and IAT in BAO, a randomized trial comparing the 2 may need to be quite large to find a significant difference in functional outcome variables. Nevertheless, such a trial is needed, the time to perform it has come, and with the combined efforts of some larger centers, it can be achieved. In most centers with interventional neuroradiologists, IAT is combined with a novel armamentarium of mechanical recanalization techniques. Therefore, a trial for BAO treatment will have to compare IVT and endovascular recanalization (all used combinations of IAT and mechanical recanalization) and a third arm of a combined IVT/IAT approach. Such a trial will probably not give a
simple answer. However, most likely, it will tell us which patient will potentially derive the most benefit from an intravenous, endovascular, or a combined treatment approach. Should a trial be unrealistic, an international registry with standardized patient selection criteria might also be helpful.

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