ABSTRACT
Background We evaluated safety and efficacy of intravenous recombinant tissue plasminogen activator plus endovascular (bridging) therapy compared with direct endovascular therapy in patients with ischaemic stroke due to basilar artery occlusion (BAO).

Methods From a national prospective registry of endovascular therapy in acute ischaemic stroke, we selected patients with BAO. We compared bridging and direct endovascular therapy evaluating vessel recanalisation, haemorrhagic transformation at 24–36 hours; procedural complications; and functional outcome at 3 months according to the modified Rankin Scale. We ran logistic and ordinal regression models adjusting for age, sex, National Institutes of Health Stroke Scale (NIHSS), onset-to-groin-puncture time.

Results We included 464 patients, mean (±SD) age 67.7 (±13.3) years, 279 (63%) males, median (IQR) NIHSS = 18 (10–30); 166 (35%) received bridging and 298 (65%) direct endovascular therapy. Recanalisation rates and symptomatic intracerebral haemorrhage were similar in both groups (83% and 3%, respectively), whereas distal embolisation was more frequent in patients treated with direct endovascular therapy (9% vs 3%; P = 0.009). In the whole population, there was no difference between bridging and direct endovascular therapy regarding functional outcome at 3 months (OR = 0.79; 95% CI = 0.55 to 1.13). However, in patients with onset-to-groin-puncture time ≤6 hours, bridging therapy was associated with lower mortality (OR = 0.53; 95% CI = 0.30 to 0.97) and a shift towards better functional outcome in ordinal analysis (OR = 0.65; 95% CI = 0.42 to 0.98).

Conclusions In ischaemic stroke due to BAO, when endovascular therapy is initiated within 6 hours from symptoms onset, bridging therapy resulted in lower mortality and better functional outcome compared with direct endovascular therapy.

INTRODUCTION
Endovascular treatment for acute ischaemic stroke gained wide acceptance for anterior ischaemic stroke caused by intracranial large vessel occlusion. More than 80% of patients enrolled in major endovascular clinical trials received intravenous treatment with recombinant tissue plasminogen activator (rt-PA) before endovascular treatment, supporting the use of rt-PA before endovascular treatment.

However, patients with ischaemic stroke and posterior circulation symptoms were excluded from the aforementioned clinical trials. Unlike the anterior circulation, the posterior circulation depends on the basilar artery, which supplies most of the brainstem, part of the cerebellum, thalamus and the occipital lobes. Ischaemic stroke in the posterior circulation stroke represents about 20% of all ischaemic strokes and is a major challenge due to the variability of clinical presentation, ranging from transient ischaemic attack or minor stroke to rapidly progressive brainstem dysfunction or coma at onset, as often seen in basilar artery occlusion (BAO). Although BAO is relatively rare, accounting for approximately 1% of all ischaemic strokes and 5%–10% of large vessel occlusion strokes, it is a subtype of ischaemic stroke with a rate of disability and mortality of almost 80%. Moreover, there is debate about the best acute treatment strategy (only rt-PA, direct endovascular, both) in BAO and evidence about the acute management for BAO is lacking.

The per-protocol and the as-treated analysis of the recent BEST trial seemed to favour endovascular treatment, although the intention-to-treat analysis was neutral. A subgroup analysis of the recent BASICS trial suggested that endovascular treatment was effective in patients with moderate to severe neurological deficit, whereas rt-PA alone may be suitable for patients with milder deficit. Previously, the BASICS registry did not provide evidence about superiority of a treatment strategy but confirmed the high rates of mortality and disability of BAO. The American Heart Association (AHA) Guidelines suggest that endovascular treatment of BAO within 6 hours from symptoms onset is reasonable. Furthermore, there is no consensus about the treatment time window in BAO. Although AHA guidelines suggest that treatment could be reasonable within 6 hours, there is preliminary evidence that selected patients could benefit from treatment in extended time windows. Mainly based on empirical evidence, many centres with endovascular therapy service adopted revascularisation protocols for BAO with wider time windows than those recommended for endovascular therapy.

The aim of the present study, based on a prospective national registry of patients with ischaemic stroke receiving endovascular treatment, was to explore in those with BAO safety and efficacy of...
RESULTS

General characteristics
In the study period, data about 728 patients with occlusion in the posterior circulation were available from the registry. A total of 61 (8%) patients had posterior cerebral artery occlusion and 49 (7%) had vertebral artery occlusion and were excluded, further 127 (17%) patients had no available relevant anamnesis/clinical data or had combined basilar + vertebral or basilar + posterior cerebral artery occlusions, and 25 (3%) had missing mRS at 3 months and were therefore excluded from the final analysis. Among the remaining 466 patients with isolated BAO treated with endovascular therapy, we had two missing data about type of treatment, which left 464 patients for the final analysis (figure 1).

Baseline characteristics of the study population are summarised in table 1. Mean (±SD) age was 67.7 (±13.3) years, 303 (65%) patients were male, 166 (36%) received bridging and 298 (64%) direct endovascular therapy. Overall, 36 (8%) of patients had MR before endovascular treatment, the remaining patients were male, 166 (36%) received bridging and 298 (64%) direct endovascular therapy. Overall, 36 (8%) of patients had MR before endovascular treatment, the remaining patients were male, 166 (36%) received bridging and 298 (64%) direct endovascular therapy. Overall, 36 (8%) of patients had MR before endovascular treatment, the remaining patients were male, 166 (36%) received bridging and 298 (64%) direct endovascular therapy. Overall, 36 (8%) of patients had MR before endovascular treatment, the remaining patients were male, 166 (36%) received bridging and 298 (64%) direct endovascular therapy. Overall, 36 (8%) of patients had MR before endovascular treatment, the remaining patients were male, 166 (36%) received bridging and 298 (64%) direct endovascular therapy. Overall, 36 (8%) of patients had MR before endovascular treatment, the remaining patients were male, 166 (36%) received bridging and 298 (64%) direct endovascular therapy. Overall, 36 (8%) of patients had MR before endovascular treatment, the remaining patients were male, 166 (36%) received bridging and 298 (64%) direct endovascular therapy. Overall, 36 (8%) of patients had MR before endovascular treatment, the remaining patients were male, 166 (36%) received bridging and 298 (64%) direct endovascular therapy. Overall, 36 (8%) of patients had MR before endovascular treatment, the remaining patients were male, 166 (36%) received bridging and 298 (64%) direct endovascular therapy. Overall, 36 (8%) of patients had MR before endovascular treatment, the remaining patients were male, 166 (36%) received bridging and 298 (64%) direct endovascular therapy. Overall, 36 (8%) of patients had MR before endovascular treatment, the remaining patients were male, 166 (36%) received bridging and 298 (64%) direct endovascular therapy. Overall, 36 (8%) of patients had MR before endovascular treatment, the remaining patients were male, 166 (36%) received bridging and 298 (64%) direct endovascular therapy. Overall, 36 (8%) of patients had MR before endovascular treatment, the remaining patients were male, 166 (36%) received bridging and 298 (64%) direct endovascular therapy. Overall, 36 (8%) of patients had MR before endovascular treatment, the remaining patients were male, 166 (36%) received bridging and 298 (64%) direct endovascular therapy. Overall, 36 (8%) of patients had MR before endovascular treatment, the remaining patients were male, 166 (36%) received bridging and 298 (64%) direct endovascular therapy. Overall, 36 (8%) of patients had MR before endovascular treatment, the remaining patients were male, 166 (36%) received bridging and 298 (64%) direct endovascular therapy. Overall, 36 (8%) of patients had MR before endovascular treatment, the remaining patients were male, 166 (36%) received bridging and 298 (64%) direct endovascular therapy. Overall, 36 (8%) of patients had MR before endovascular treatment, the remaining patients were male, 166 (36%) received bridging and 298 (64%) direct endovascular therapy. Overall, 36 (8%) of patients had MR before endovascular treatment, the remaining patients were male, 166 (36%) received bridging and 298 (64%) direct endovascular therapy. Overall, 36 (8%) of patients had MR before endovascular treatment, the remaining patients were male, 166 (36%) received bridging and 298 (64%) direct endovascular therapy. Overall, 36 (8%) of patients had MR before endovascular treatment, the remaining patients were male, 166 (36%) received bridging and 298 (64%) direct endovascular therapy. Overall, 36 (8%) of patients had MR before endovascular treatment, the remaining patients were male, 166 (36%) received bridging and 298 (64%) direct endovascular therapy. Overall, 36 (8%) of patients had MR before endovascular treatment, the remaining patients were male, 166 (36%) received bridging and 298 (64%) direct endovascular therapy. Overall, 36 (8%) of patients had MR before endovascular treatment, the remaining patients were male, 166 (36%) received bridging and 298 (64%) direct endovascular therapy. Overall, 36 (8%) of patients had MR before endovascular treatment, the remaining patients were male, 166 (36%) received bridging and 298 (64%) direct endovascular therapy.
Cerebrovascular disease

728 patients with occlusion in the posterior circulation

- 110 (15%) patients did not have BAO:
  - 61 PCA occlusion
  - 49 VA occlusion

618 patients with BAO

- 127 (17%) patients excluded for:
  - Incomplete clinical or anamnestic data
  - Combined occlusion (BAO + PCA or BAO + VA occlusion)

25 (3%) missing mRS at three months

2 missing treatment type

464 patients with BAO included in final analysis

Figure 1 Flow diagram of study population. BAO, basilar artery occlusion; mRS, modified Rankin Scale; PCA, posterior cerebral artery; VA, vertebral artery.

treated with direct endovascular therapy had higher NIHSS (18 vs 17; p=0.038), were more likely to have atrial fibrillation (26% vs 13%; p<0.001) and were more frequently on therapy with antiplatelets (33% vs 24%; p=0.025) and anticoagulants (11% vs 7%; p=0.064) before stroke. There was no difference between bridging and direct endovascular regarding onset-to-groin-puncture (280 vs 300 min, respectively; p=0.175) and duration of endovascular treatment (80 vs 79 min, respectively; p=0.451). There were no other differences among general characteristics of the population. Characteristics of study population stratified by onset to endovascular treatment time (≤ and > 6 hours) are shown in online supplemental tables 1, 2 A, B.

Efficacy outcomes

Good recanalisation (TICI 2b/3) of basilar artery was obtained in 375 (82%) patients, with no differences between bridging and endovascular treatment (83% vs 81%, respectively; p=0.857; online supplemental figure 1). At 3 months, a total of 115 (25%) patients had died, 176 (38%) had excellent (mRS=0–1) and 215 (46%) had good outcome (mRS=0–2). Patients treated with bridging therapy had more frequently excellent outcome (43% vs 35%; p=0.070) and good outcome (53% vs 43%; p=0.031); but the associations were not confirmed in multivariable logistic regression analysis (OR=1.21; 95% CI=0.78 to 1.87; OR=1.35; 95% CI=0.88 to 2.08; respectively; online supplemental table)
Similarly, bridging therapy was associated with lower occurrence of death at 3 months (19% vs 28%; p = 0.028), but the association was not confirmed after adjustment for confounders (OR = 0.68; 95% CI = 0.41 to 1.22) (table 2). In ordinal shift analysis, after adjustment for confounders, we did not find an association between type of treatment and functional outcome (common OR = 0.79; 95% CI = 0.53 to 1.13) (figure 3).

We therefore stratified the study population according to the endovascular time window of 6 hours, and found 301 (65%) patients with onset-to-groin-puncture within 6 hours (116 bridging treatment, 185 direct endovascular) and 135 (29%) patients with onset-to-groin-puncture beyond 6 hours (43 patients with bridging and 92 with endovascular treatment). 28 (6%) patients had missing onset-to-groin-puncture time and two types of treatment data. Patients treated with endovascular therapy within 6 hours were older compared with patients treated after 6 hours, there were no other differences among baseline characteristics between the two groups online supplemental table 1. Patients treated with bridging therapy within 6 hours had higher but not statistically significant chances to achieve excellent outcome (43% vs 35%; p = 0.139) and good outcome (55% vs 42%; p = 0.028) compared with those treated with direct endovascular treatment. However, the latter association was not confirmed in multivariate analysis (OR = 1.60; 95% CI = 0.97 to 2.65). Similarly, patients treated with bridging therapy within 6 hours had reduced risk of death at 3 months (19% vs 30%; p = 0.019), this association was confirmed after adjustment for confounders (OR = 0.53; 95% CI = 0.30 to 0.97) (table 2). In patients treated within 6 hours from symptoms onset, after adjustment for confounders in ordinal shift analysis, bridging therapy was associated with a shift towards better functional outcomes at 3 months (common OR = 0.65; 95% CI = 0.42 to 0.98) (figure 4A). We did not find any association in patients treated beyond 6 hours from symptoms onset (figure 4B). Further analyses are shown in online supplemental material. Further analyses showing functional outcomes at 3 months and recanalisation rate stratified by BAO occlusion site are shown in online supplemental tables 4 and 5.

### Safety outcomes

A total of 51 (12%) patients had HT of any type with higher frequency in patients treated with bridging therapy (17% vs 9%; p = 0.011); whereas sICH occurred in 17 (4%) patients, with no difference between bridging and direct endovascular therapy (4% vs 4%; p = 0.605) (table 3). There were no differences between the two groups in procedural complications, except higher rates of distal embolisation/thrombus fragmentation in patients treated with direct endovascular therapy (9% vs 3%; p = 0.009) (table 4).

### Table 2: Functional outcomes at 3 months in the whole population and stratified by onset to groin puncture time

<table>
<thead>
<tr>
<th>Time window</th>
<th>Total</th>
<th>Bridging</th>
<th>Endovascular</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;6 hours</td>
<td>mRS 0–1</td>
<td>176 (38)</td>
<td>72 (43)</td>
<td>104 (35)</td>
<td>1.43 (0.97 to 2.10)</td>
</tr>
<tr>
<td></td>
<td>mRS 0–2</td>
<td>215 (46)</td>
<td>88 (53)</td>
<td>127 (43)</td>
<td>1.52 (1.04 to 2.23)</td>
</tr>
<tr>
<td></td>
<td>Death</td>
<td>114 (25)</td>
<td>31 (19)</td>
<td>83 (28)</td>
<td>0.60 (0.37 to 0.95)</td>
</tr>
<tr>
<td>≤6 hours</td>
<td>mRS 0–1</td>
<td>114 (38)</td>
<td>50 (43)</td>
<td>64 (35)</td>
<td>1.43 (0.89 to 2.30)</td>
</tr>
<tr>
<td></td>
<td>mRS 0–2</td>
<td>142 (47)</td>
<td>64 (55)</td>
<td>78 (42)</td>
<td>1.69 (1.06 to 2.70)</td>
</tr>
<tr>
<td></td>
<td>Death</td>
<td>77 (26)</td>
<td>21 (19)</td>
<td>56 (30)</td>
<td>0.51 (0.29 to 0.90)</td>
</tr>
</tbody>
</table>

Analysis adjusted for: age, sex, NIHSS, onset-to-groin-puncture.

*Twenty-eight patients missing onset-to-groin puncture time.

mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.
therapy in patients with anterior large vessel occlusion due could be possibly more effective compared with bridging when endovascular treatment was initiated within 6 hours had lower mortality and a shift towards better functional outcome compared with those treated with direct endovascular therapy. This association was not observed in patients with onset-to-groin puncture beyond 6 hours.

Although BAO is a rare event, its natural history is associated with poor outcomes and acute treatment is fundamental to reduce disability and mortality. Due to the lack of conclusive evidence from randomised controlled trials, there is still uncertainty about the best management of acute BAO. Prospective studies did not favour any specific acute treatment strategy, while a meta-analysis of cohort studies and a recent randomised trial would suggest a potential benefit of endovascular treatment (bridging or direct) over intravenous thrombolysis alone. Such finding is in keeping with a subgroup analysis of the BASICS trial that showed a benefit of endovascular therapy over best medical treatment in patients with NIHSS >10, although the trial was overall neutral. Moreover, a recent study showed a greater benefit of endovascular therapy over standard medical therapy. In line with these findings, our results suggest a greater efficacy in terms of functional outcome of bridging (rt-PA + endovascular) approach compared with direct endovascular strategy (endovascular only) in acute management of BAO. We found that recanalisation rate was similar to previous studies, with little difference between bridging and direct endovascular treatment, and the duration of the endovascular procedure was similar in both groups. However, the bridging group achieved better functional outcomes, which was statistically significant when endovascular treatment was initiated within 6 hours from symptoms onset.

Some authors suggested that direct endovascular therapy could be possibly more effective compared with bridging therapy in patients with anterior large vessel occlusion due to higher haemorrhagic risk, distal thrombus migration and delay of endovascular therapy initiation in bridging therapy. A recent randomised controlled trial showed non-inferiority of direct endovascular compared with bridging treatment within 4.5 hours from symptoms onset, however, patients had occlusion in the anterior circulation. There are scarce data about comparison of bridging versus direct endovascular therapy in the posterior circulation, and our results did not advocate direct endovascular therapy in patients with BAO. Although there was an increase in HT in the bridging therapy group, sICH occurrence was similar in both groups and to that reported in previous studies. Interestingly, in the BASICS trial rt-PA was administered in around 80% of patients allocated to the endovascular group, and the reported occurrence of sICH was approximately the same with that of our study. We did not observe a longer time to treatment in patients treated with bridging therapy, and this does not support the issue of a delay of endovascular therapy initiation in patients treated with bridging therapy. However, around one-third of patients with onset-to-groin puncture beyond 6 hours received rt-PA, suggesting a delay of the in-hospital workflow of more than 1 hour from rt-PA to groin puncture in some patients. On the other hand, it should be noted that the onset-to-groin puncture was similar to other data on BAO. Conversely to previous observations, we found a higher occurrence of distal embolisation in the direct endovascular group, suggesting that rt-PA before endovascular therapy may help lysing thrombus, rather than facilitating migration in small distal arteries not accessible with endovascular procedures. Our findings are also in keeping with previous studies that demonstrated better functional outcomes of bridging therapy in anterior circulation stroke and reinforce the indication of rt-PA before endovascular treatment also in patients with BAO. While mortality was lower in bridging therapy within 6 hours from symptoms onset, beyond 6 hours it was approximately the same in the two groups. This supports previous studies that found that time to treatment is crucial also in posterior circulation stroke, suggesting that appropriate selection of patients eligible for recanalisation treatment beyond 6 hours may help to improve functional outcomes. Although our data suggest that bridging therapy is safe and improves functional outcomes compared with direct endovascular, it is still unknown whether administration of thrombolytic therapy beyond 4.5 hours in the posterior circulation, particularly BAO, is safe and effective.

Our study has limitations. As an observational registry, patients were not randomised but were allocated according to eligibility to rt-PA or not, and this may have introduced a selection bias not detectable even with adjustment in the multivariable analysis. Furthermore, if patients with missing anamnestic, clinical and outcome data have had more severe strokes, we could expect another selection bias. Our findings are therefore hypothesis generating and add to the existing evidence from other observational studies, but need confirmation in external cohorts. Again, a detection bias in assessment of recanalisation and outcomes is also plausible, since we were not blinded to treatment allocation. Moreover, our registry did not record prognostic radiological variables such as posterior circulation Alberta Stroke Programme Early CT Score, which has been shown to reliably predict outcomes in patients with stroke due to posterior occlusion. However, all such limitations could represent a reasonable trade-off for including a relevant sample size from a prospective national registry. We included patients treated in the context of a multicentre collaboration in a timeframe of 7 years, with a considerable proportion of patients treated before the publication of trials that demonstrated efficacy of endovascular therapy. As a consequence, some patients were likely treated with

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Haemorrhagic transformation at 24 hours after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total*</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>N=443</td>
</tr>
<tr>
<td>Any ICH</td>
<td>17 (4)</td>
</tr>
<tr>
<td>All ICH</td>
<td>51 (12)</td>
</tr>
<tr>
<td>Values are number (%). *Twenty-one patients missing data. ICH, intracerebral haemorrhage.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Procedural complications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>SAH—perforation</td>
<td>14 (3)</td>
</tr>
<tr>
<td>Dissection</td>
<td>11 (2)</td>
</tr>
<tr>
<td>Fragmentation/embolisation</td>
<td>32 (7)</td>
</tr>
<tr>
<td>Other complications*</td>
<td>14 (3)</td>
</tr>
<tr>
<td>Values are number (%). *Forty-seven patients missing data. SAH, subarachnoid haemorrhage.</td>
<td></td>
</tr>
</tbody>
</table>
older endovascular devices and different procedures; in-hospital workflows may also vary, since from 2015 endovascular trials prompt implementation of strategies to reduce prehospital and in-hospital processes. However, we analysed a large sample size that reflects the real-world population and pragmatic treatment of acute stroke. We did not include in our analysis patients with BA0 treated only with rt-PA that experienced an early improvement and were not treated with endovascular procedures, thus another selection bias is possible. However, this would have favoured the endovascular rather than the bridging approach group, since around 10% of candidates to endovascular treatment have an early vessel recanalisation and neurological improvement when treated with systemic thrombolysis that avoid further treatment. \[15\] \[16\]

In conclusion, our results suggest that patients with ischaemic stroke due to BA0 bridging therapy have less thrombus fragmentation and distal embolisation compared with direct endovascular treatment, and when initiated within 6 hours from symptoms onset, is associated with reduced mortality and improved functional outcomes. Similar to indications for anterior circulation strokes, our results support early treatment and administration of intravenous thrombolysis prior to endovascular treatment for BA0. Further studies with appropriate design are warranted to replicate our findings and to clarify whether patients with appropriate selection may benefit from bridging or direct endovascular therapy with extended treatment time.

**Collaborators**

Italian Registry of Endovascular Treatment in Acute Stroke (IETAS)

Study Group: Antonio Lasio; Carolina Caprini; Enrico Fainardi; Patrizia Nencini; Fabrizio Sallustio; Daniele Morosetti; Stefano Vallone; Guido Bigliardi; Sergio Study Group; Antonio Laiso; Carolina Capirossi; Patrizia Nencini; ORCID iDs

Sergio Nappini http://orcid.org/0000-0002-2607-5815

Francesco Arba http://orcid.org/0000-0003-3941-7383

**References**


Cerebrovascular disease