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Background and Purpose—The frequent use of a longer time window for recanalization therapy in patients with basilar artery occlusion (BAO) in daily practice is not supported by any scientific evidence. We investigated the relationship between time to recanalization therapy and functional outcome in BAO with data from the Basilar Artery International Cooperation Study (BASICS).

Methods—BASICS is a prospective multicenter registry of patients (n=619) with radiologically confirmed BAO. We analyzed patients receiving intravenous thrombolysis or intra-arterial treatment. Patients were divided into 4 groups based on the interval between estimated time of BAO and start of recanalization therapy: ≤3 hours (n=134), >3 to ≤6 hours (n=151), >6 to ≤9 hours (n=56), and >9 hours (n=68). Primary outcome measure was poor functional outcome (modified Rankin scale score 4–6) after 1 month. We calculated adjusted risk ratios with 95% CIs using Poisson regression analyses with the ≤3 hours group as the reference group.

Results—Patients had an increased risk of poor functional outcome as time to recanalization therapy became longer (≤3 hours: 62%; >3 to ≤6 hours: 67% [adjusted risk ratio, 1.06; 0.91–1.25]; >6 to ≤9 hours: 77% [adjusted risk ratio, 1.26; 1.06–1.51]; >9 hours: 85% [adjusted risk ratio, 1.47; 1.26–1.72]).

Conclusions—Early recanalization therapy in patients with BAO is associated with a more favorable outcome with a significant increased chance of a poor outcome when recanalization therapy is started >6 hours after estimated time of BAO. (***Stroke***. 2012;43:3003-3006.)

Key Words: basilar artery occlusion ■ ischemic stroke ■ outcome ■ recanalization therapy ■ thrombolysis
■ time is brain

P atients with acute ischemic stroke in the anterior circulation benefit from intravenous thrombolysis (IVT) within 4.5 hours after symptom onset.[1] The earlier IVT can be administered, the more benefit can be expected. Intra-arterial thrombolysis might even be effective when patients are treated within 6 hours.[2] It remains unknown whether the time window for recanalization therapy in patients with basilar artery occlusion (BAO) can be longer than in patients with arterial occlusions in the anterior circulation.[3] White matter, which is relatively more present in the brain stem than in other parts of the brain, might be more resistant to ischemia than other brain tissue. Furthermore, penumbral tissue might be preserved for a longer period of time as a result of better collaterals in the posterior than in the anterior circulation.

Case reports suggest that patients with BAO can recover from recanalization therapy beyond 8 hours after symptom onset.[4]

We aimed to study the relationship between time to recanalization therapy and functional outcome in patients with acute BAO who participated in the Basilar Artery International Cooperation Study (BASICS).

Methods

BASICS is a prospective, observational registry of 619 consecutive patients ≥18 years with an acute symptomatic BAO (see online-only Data Supplement).[3] The protocol was approved by the ethics committee of the University Medical Center Utrecht, Utrecht, The Netherlands. For the purpose of the present study we excluded patients receiving no treatment and those who were treated with platelet aggregation inhibitors or heparin only. Recanalization therapy

was defined as IVT or any intra-arterial treatment (intra-arterial thrombolysis, mechanical clot disruption, or both). Time to recanalization therapy was defined as the interval between estimated time of BAO and start of recanalization therapy. Estimated time of BAO was defined as time of onset of acute symptoms leading to clinical diagnosis of BAO or, if not known, last time the patient was seen normal before onset of these symptoms. Patients were divided into 4 groups based on time to recanalization therapy: ≤3 hours, >3 to ≤6 hours, >6 to ≤9 hours, and >9 hours.

Primary outcome was poor functional outcome (modified Rankin Scale score 4–6) after 1 month. We also investigated if our conclusions changed if poor functional outcome was defined as modified Rankin Scale 3 to 6. Secondary outcomes were death and insufficient vessel recanalization (defined as Thrombolysis In Myocardial Infarction score 0–1). A sensitivity analysis was performed to investigate if our primary outcome was similar if patients were excluded with unknown time of onset of acute symptoms leading to a clinical diagnosis of BAO (for example, patients with wake-up stroke). Furthermore, we analyzed time as a linear factor with the 4 time to recanalization therapy groups. In a subgroup analysis, we studied the incidence of poor functional outcome in patients with severe and mild to moderate strokes. Severe stroke was defined as patients in a coma, with tetraplegia, or in a locked-in state, whereas mild to moderate stroke was defined as any deficit that was less severe.[5]

Outcomes were compared among the 4 groups. Risk ratios with 95% CIs were calculated with the ≤3 hours group as the reference group. Variables associated with functional outcome in the BASICS registry (ie, age, National Institutes of Health Stroke Scale score, diabetes mellitus, prodromes, and location of occlusion)[5] were used simultaneously in Poisson regression analyses to calculate adjusted risk ratios (aRRs).

Results

We included 409 patients (≤3 hours: n=134; >3 to ≤6 hours: n=151; >6 to ≤9 hours: n=56; and >9 hours: n=68). Baseline characteristics are listed in the Table.The risk of poor functional outcome increased when time to recanalization therapy was longer (≤3 hours: 62%; >3 to ≤6 hours: 67% [aRR, 1.06; 0.91–1.25]; >6 to ≤9 hours: 77% [aRR, 1.26; 1.06–1.51]; and >9 hours: 85% [aRR, 1.47; 1.26–1.72]; Table; and Figure 1). In a sensitivity analysis that excluded 24 patients in which time of symptom onset leading to a clinical diagnosis of BAO was unknown, the risk of poor functional outcome was similar (≤3 hours: 62%; >3 to ≤6 hours: 67% [aRR, 1.06; 0.91–1.25]; >6 to ≤9 hours: 76% [aRR, 1.25; 1.04–1.50]; and >9 hours: 87% [aRR, 1.48; 1.26–1.74]). If the 4 time to recanalization

therapy categories were taken as a continuous variable (with ≤3 hours=0, >3 to ≤6 hours=1, >6 to ≤9 hours=2, and >9 hours=3), the risk ratio for increase to a later time to recanalization therapy class was 1.14 (95% CI, 1.09–1.20; *P*<0.001; adjusted for National Institutes of Health Stroke Scale score, diabetes mellitus, prodromes, and location of occlusion) indicating a strong, statistically significant relationship between time to recanalization therapy and poor outcome. Also when poor outcome was defined as a modified Rankin Scale of 3 to 6 instead of 4 to 6, risk of poor functional outcome increased when time to recanalization therapy was longer (≤3 hours: 71%; >3 to ≤6 hours: 74% [aRR, 1.02; 0.90–1.17]; >6 to ≤9 hours: 89% [aRR, 1.27; 1.10–1.45]; and >9 hours: 91% [aRR, 1.35; 1.18–1.53]).

A time-dependent relationship was observed between time to recanalization therapy and risk of death (≤3 hours: 36%; >3 to ≤6 hours: 38% [aRR, 1.05; 0.79–1.41]; >6 to ≤9 hours: 39% [aRR, 1.18; 0.82–1.71]; >9 hours: 46% [aRR, 1.44; 1.05–1.99]). Similarly, a time-dependent relationship was observed between time to recanalization therapy and risk of insufficient recanalization (≤3 hours: 15 of 89 [17%]; >3 to ≤6 hours: 26 of 116 [22%] [aRR, 1.32; 0.75–2.31]; >6 to ≤9 hours: 14 of 45 [31%] [aRR, 1.87; 0.99–3.50]; >9 hours: 14 of [48] [29%] [aRR, 2.00; 1.04–3.84]).

The incidence of poor functional outcome according to stroke severity is shown in Figures 2 and 3. In patients with severe strokes at presentation, all patients treated >9 hours after symptom onset had poor functional outcome (≤3 hours: 71%; >3 to ≤6 hours: 77% [aRR, 1.07; 0.91–1.25]; >6 to ≤9 hours: 88% [aRR, 1.28; 1.08–1.51]; and >9 hours: 100% [aRR, 1.43; 1.25–1.63]). In patients with mild to moderate strokes, the risk of poor functional outcome was as follows: ≤3 hours: 42%; >3 to ≤6 hours: 49% (aRR, 1.10; 0.71–1.70); >6 to ≤9 hours: 50% (aRR, 1.10; 0.63–1.90); and >9 hours: 63% (aRR, 1.61; 1.01–2.56).

Discussion

Our study shows that in patients with BAO the risk of poor functional outcome, death, and insufficient recanalization increases when time to recanalization therapy is longer. Absolute risks were highest for those treated >9 hours, also
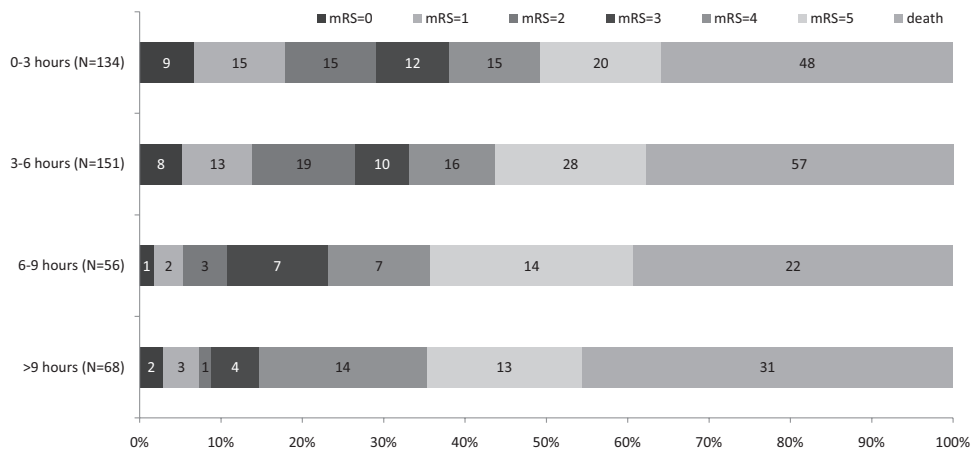

Figure 1. Functional outcome according to time to treatment.

Table. Baseline Characteristics and Poor Functional Outcome (mRS 4–6) According to Time to Treatment

	0 to 3 h* (N=134)	3 to 6 h (N=151)	6 to 9 h (N=56)	>9 h (N=68)
Median age, y (IQR)	67 (57–75)	66 (55–75)	62 (50–73)	63 (50–72)
Median NIHSS (IQR)	25 (15–30)	24 (14–30)	25 (15–30)	19 (12–27)
Diabetes mellitus	23 (17%)	35 (23%)	11 (20%)	16 (24%)
Prodromes	55 (41%)	78 (52%)	33 (59%)	38 (56%)
Location of occlusion				
Distal third	48 (36%)	53 (35%)	19 (34%)	17 (25%)
Middle third	30 (22%)	41 (27%)	11 (20%)	15 (22%)
Proximal third	56 (42%)	57 (38%)	26 (46%)	36 (53%)
Poor functional outcome	83 (62%)	101 (67%)	43 (77%)	58 (85%)
Unadjusted risk ratio	1	1.08 (0.91–1.29)	1.24 (1.02–1.51)	1.38 (1.17–1.63)
Adjusted risk ratios				
Age	1	1.09 (0.92–1.29)	1.29 (1.06–1.57)	1.45 (1.23–1.70)
NIHSS	1	1.08 (0.91–1.27)	1.24 (1.03–1.49)	1.48 (1.27–1.72)
Diabetes mellitus	1	1.07 (0.90–1.27)	1.24 (1.02–1.50)	1.36 (1.16–1.61)
Prodromes	1	1.06 (0.89–1.27)	1.21 (0.99–1.47)	1.35 (1.14–1.59)
Location of occlusion	1	1.08 (0.91–1.29)	1.23 (1.02–1.49)	1.35 (1.14–1.59)
All 5 factors	1	1.06 (0.91–1.25)	1.26 (1.06–1.51)	1.47 (1.26–1.72)

Data are no. (%) or risk ratio (95% CI).

mRS indicates modified Rankin Scale; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale.

*Reference group.

after multivariable adjustment. All patients with severe strokes at presentation treated >9 hours after symptom onset had poor functional outcome.

Previous studies that investigated predictors of recanalization and functional outcome after BAO often dichotomized time to treatment with a cutoff of 6 hours after symptom onset.[6,7] Some studies found no association between time to treatment and recanalization or outcome.[6,7] Others found that time to treatment was a predictor of functional outcome in univariable but not in multivariable analyses.[8]

Our results imply that patients with BAO should be treated as soon as possible after symptom onset, similar to patients with ischemic stroke in the anterior circulation. Because all patients with severe stroke treated >9 hours after symptom onset had poor functional outcome, there is probably no benefit of recanalization therapy in this group of patients.

Previous studies have shown that BAO is preceded by prodromal symptoms in >60% of patients.[9,10] Most of these patients would be excluded from a potential trial that has the time of onset of any symptom to treatment as an inclusion criterion. Therefore, we used an estimated time to treatment from the onset of symptoms consistent with a clinical diagnosis of BAO rather than the more commonly used time of onset of any symptom to treatment. Our findings support the use of a more liberal definition of time of onset in patients with BAO.

Although patients treated at later time intervals tended to be younger and to have less severe stroke symptoms, these patients had a worse outcome, which was also true after correction for baseline imbalances. We did not make a distinction between patients treated with intra-arterial treatment or IVT. In a previous study we did not find significant differences between these treatment groups in various time to treatment
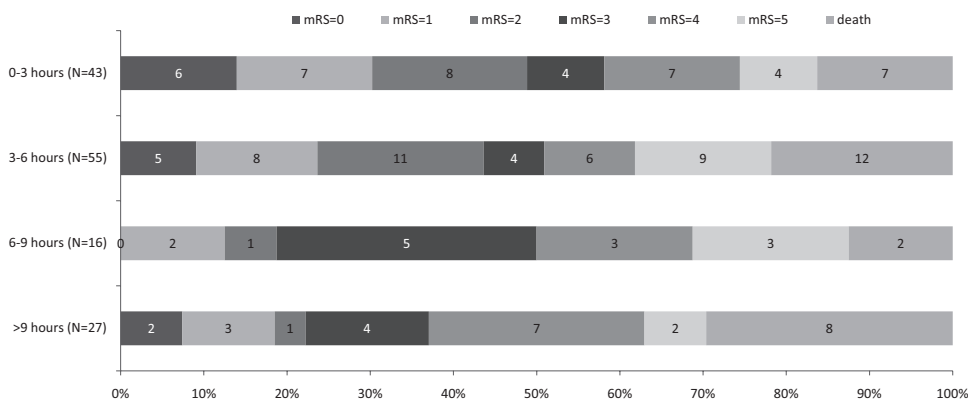
Figure 2. Functional outcome according to time to treatment in patients with mild to moderate strokes.
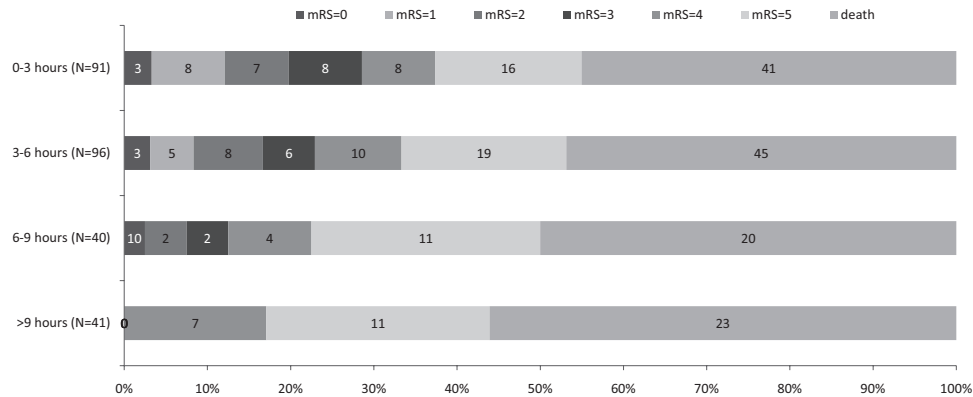
Figure 3. Functional outcome according to time to treatment in patients with severe strokes.

subcategories, which might be caused by the small number of patients in each subgroup.[5] The question of which treatment option is superior in patients with BAO will be answered by the recently started BASICS trial, in which patients are randomized between IVT alone versus IVT followed by additional intra-arterial treatment (www.basicstrial.com). In the BASICS trial, patients will only be included if initiation of intra-arterial treatment is feasible within 6 hours of estimated time of BAO. The present study shows that only 23% of patients treated between 6 and 9 hours had good functional outcome compared with 35% of patients treated within 6 hours. Including patients beyond 6 hours after estimated time of BAO in a randomized trial would dilute a potential beneficial effect and require a larger sample size.

The strength of this study is that BASICS was a prospective registry of consecutive patients and therefore our results are representative for daily practice. A limitation is that it was a post hoc analysis of nonrandomized data, and therefore the data regarding treatment-dependent outcomes are prone to bias. However, the prospective collection of detailed data allowed us to adjust for important confounding baseline characteristics.

We conclude that early recanalization therapy in patients with BAO is associated with a more favorable outcome. This implies that these patients should be treated as soon as possible. Beyond 9 hours, the prognosis of patients with severe BAO is universally dismal despite recanalization therapy.

Sources of Funding

Disclosures

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SUPPLEMENTAL MATERIAL

Participating centers (with number of patients and names of investigators)

Participating centers (with number of patients and names of investigators) were as follows. Australia (6): University of Melbourne (A.M. Weber, G.A. Donnan); Belgium (21): University Hospital, Leuven (11; V. Thijs), University Hospital St. Luc, Brussels (10; A. Peeters); Brazil (18): University of Rio de Janeiro (11; G. de Freitas), University of Sao Paolo, Hospital das Clinicas (5; A.B. Conforto), Federal University of Sao Paolo (2; M. Miranda-Alves, A. Massaro); Finland (14): University of Helsinki (14; P. Ijäs, T. Bogoslovsky, P.J. Lindsberg); Germany (224): German Stroke Database (77; C. Weimar, J. Benemann, K. Kraywinkel), University Hospital Freiburg (20; C. Haverkamp), Leipzig University (15; D. Michalski), University Hospital Essen (10; C. Weimar), Medical University Hannover (8; K. Weissenborn), 6; University Hospital, Magdeburg (M. Goertler), 4; University Hospital Rostock (A. Kloth), Kliniken Neuruppin (3; A. Bitsch), Bürger Hospital, Stuttgart (3; T. Mieck), Heinrich Braun Krankenhaus, Zwickau (2; J. Machetanz), Sofien and Hufeland Hospital, Weimar (2; P. Möller), University Hospital, Ulm (2; R. Huber), Hospital Heidenheim (2; S. Kaendler), St. Elisabeth Hospital, Ravensburg (47; C. Rueckert), TEMPiS Network Bavaria (38; H. Audebert, R. Müller, B. Vatankhah), University of Munich (26; T. Pfefferkorn, T.E. Mayer), Universitätsklinikum Mannheim (19; K. Szabo), Dresden University (13; C. Disque), Klinikum Minden (2; O. Busse), University of Heidelberg (2; C. Berger, W. Hacke); Israel (19): Sheba Medical Center (19; Y. Schwammenthal, D. Orion, D. Tanne); Italy (6): University of Turin (5; M. Bergui), University of Bologna (1; E. Pozzati); Netherlands (82): St. Antonius Hospital, Nieuwegein (40; W.J. Schonewille), University Medical Center Utrecht (22; W.J. Schonewille, A. Algra,

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