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Review article

Treatment of acute basilar artery occlusion: Systematic review and meta-analysis

Adam Wyszomirski, Sebastian Szczyrba, Dominika Tomaka, Bartosz Karaszewski *

Department of Adult Neurology, Medical University of Gdansk and University Clinical Centre in Gdansk, ul. Dębinki 7, 80-211 Gdańsk, Poland

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ABSTRACT

Introduction: Acute basilar artery occlusion (BAO) results in strokes characterized by poor outcome. Intravenous and intraarterial thrombolysis with rt-PA (IV rt-PA and IA rt-PA, respectively) and mechanical thrombectomy (MT) are the most commonly used techniques to treat BAO, but their efficacy remains unclear. Unlike in previous papers, we compared all three methods of the treatment in a single work, including an update of meta-analysis regarding each of the three therapeutic approaches with recent trials.

Methods: We systematically reviewed all original studies testing the efficacy of any of the three basic methods of BAO treatment dated up to the end of Jan 2017.

Results: The final analysis included 31 studies that summarized 1358 patients. These subjects were organized into three therapeutic groups: IV rt-PA, IA rt-PA ± IV rt-PA, MT ± IV rt-PA ± IA rt-PA. The weighted pooled estimates of a favorable outcome (mRS 0–2) were 32.57% (95% CI 16.44–51.03%/I^2 = 67.5%, p = 0.0795) in the first group, 22.56% (95% CI 16.85–28.79%/I^2 = 52.1%, p = 0.027) in the second group, and 37.04% (95% CI 32.27–41.92%/I^2 = 32%, p = 0.0895) in the third group. The Q-test subgroup analysis revealed the statistical superiority of MT ± IV rt-PA ± IA rt-PA over IA rt-PA ± IV rt-PA (mRS 0–2: p = 0.0003, mRS 6: p = 0.0010) and over any rt-PA administration (either IV rt-PA or IA rt-PA ± IV rt-PA) (mRS 0–2: p = 0.0006, mRS 6: p = 0.0056).

Conclusions: Current data on the effects of the three basic approaches of the treatment of BAO are insufficient to generate high-class EBM guidelines. MT seems to be the most effective method of the treatment of acute BAO. The efficacy of IV or IA thrombolytic therapy in this indication remains unclear.

* *Corresponding author at*: Department of Adult Neurology, Medical University of Gdansk & University Clinical Center in Gdansk, ul. Dębinki 7, 80-211 Gdańsk, Poland.
E-mail addresses: bartkar@gumed.edu.pl, bartosz@karaszewski.org (B. Karaszewski).

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1. Introduction

Acute basilar artery occlusion (BAO) results in strokes characterized by poor outcomes and high mortality [1]. The most commonly applied therapies for acute BAO include intravenous and/or intraarterial administration of recombinant tissue plasminogen activator (IV rt-PA and IA rt-PA, respectively) and any-device mechanical thrombectomy (MT). There are few and rather small trials investigating therapeutic approaches in acute BAO, which is partially caused by the relatively low prevalence of this condition [2–32]. Their results have been summarized and meta-analyzed in further studies [33–35]. These have suggested that mechanical thrombectomy, both in monotherapy or in combination with thrombolytic therapy, is the efficient therapeutic option in this type of stroke, whereas data for the effects of IV rt-PA and IA rt-PA are much less unequivocal [33–35].

Only a few papers provide an analytical comparison of the selected two of the three basic methods of BAO treatment, and no one lists and statistically compares all three in one dissertation, as per a PubMed search [33–36]. In this study, we performed meta-analyses of the basic common methods of the treatment of acute BAO in terms of the functional outcome,

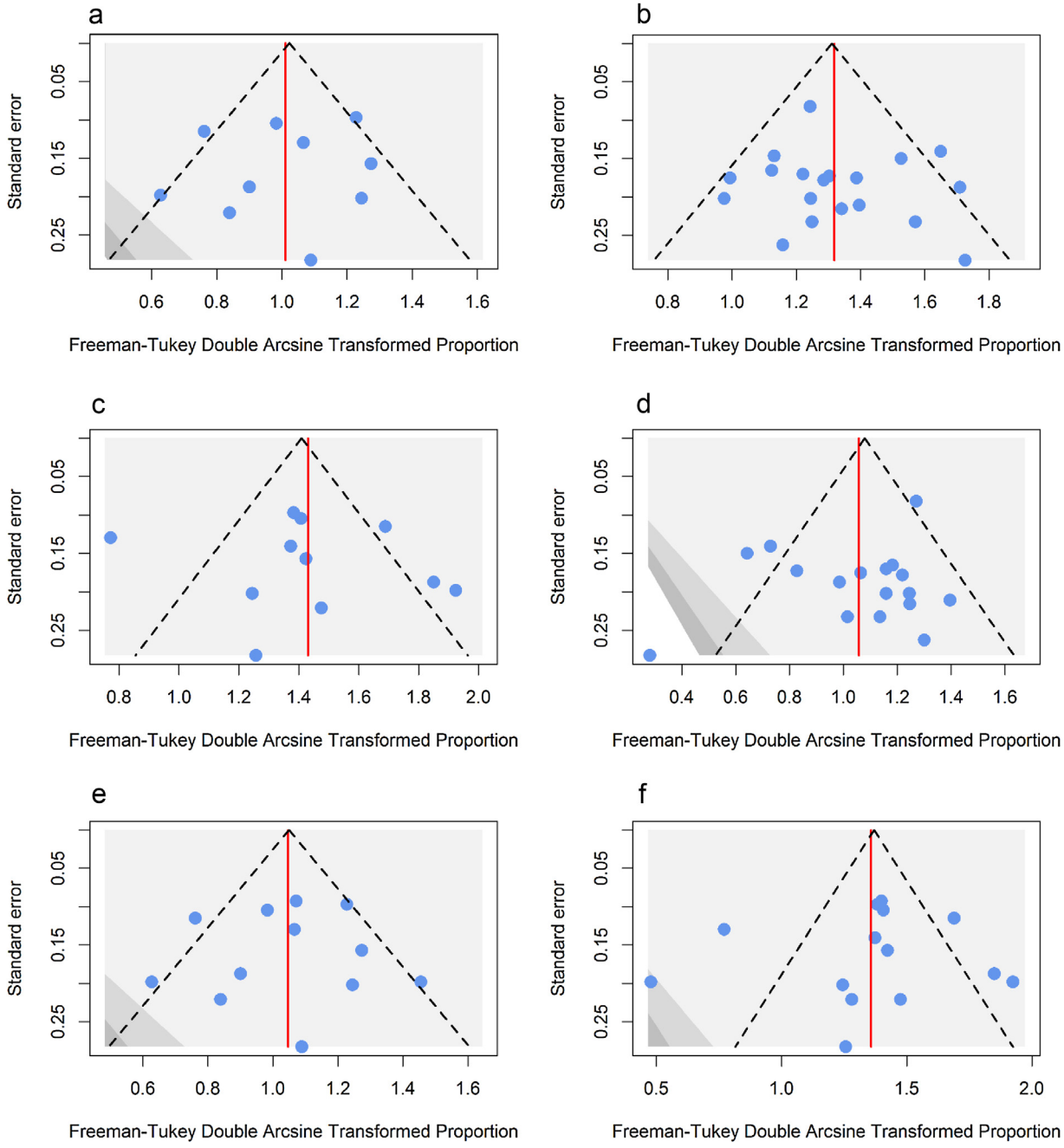


Fig. 1 – Funnel plots for (a) favorable outcome in group 2; (b) favorable outcome in group 3; (c) mortality in group 2; (d) mortality in group 3; (e) favorable outcome in groups 1 and 2; and (f) mortality in groups 1 and 2.

and separately mortality, and compared the outcomes between each of the therapeutic approaches. We accommodated all BAO therapeutic trials published or being available on-line and/or in press by the end of January 2017. These included several recent articles that have never been taken into account in any of the previous meta-analyses. We divided and combined treatment protocols used in these studies into three groups: 1/lone IV rt-PA, 2/IA rt-PA preceded or not by IV rt-PA, and 3/any-device MT preceded or not by any route of rt-PA administration.

2. Materials and methods

2.1. Study search and selection

Two of the authors (SS and DT) have independently reviewed MEDLINE (PubMed) and SCOPUS databases for suitable papers published until the end of January 2017, introducing the following search design: 'basilar [title] AND occlusion [title] AND treatment' for MEDLINE and 'TITLE (basilar) AND TITLE (occlusion) AND ALL (treatment)' for SCOPUS. Following this, the authors identified the final package for the meta-analysis based on title and abstract reads. Data inconsistencies in the selection of articles between reviewers were discussed and resolved by mutual consensus. The full texts of the selected papers were then carefully analyzed and used to do the meta-analyses.

2.2. Eligibility criteria

In the final analysis, we included observational or interventional studies, regardless of the project design, published in English, performed in an adult population, covering data about a minimum of 10 patients treated due to acute BAO, and reporting a 3-month assessment of the functional outcome by modified Rankin Scale (mRS) [37]. We excluded studies testing methods of the BAO treatment other than intravenous or intra-arterial thrombolysis with recombinant tissue plasminogen activator (rt-PA) and mechanical thrombectomy or their combinations. The main outcome measures included disability (mRS score 3 months after stroke onset) and mortality.

2.3. Treatment strategies and compared groups

We divided the selected BAO therapeutic trials and series' descriptions into three groups. The first included all studies testing the efficacy of intravenous thrombolysis alone (group 1:

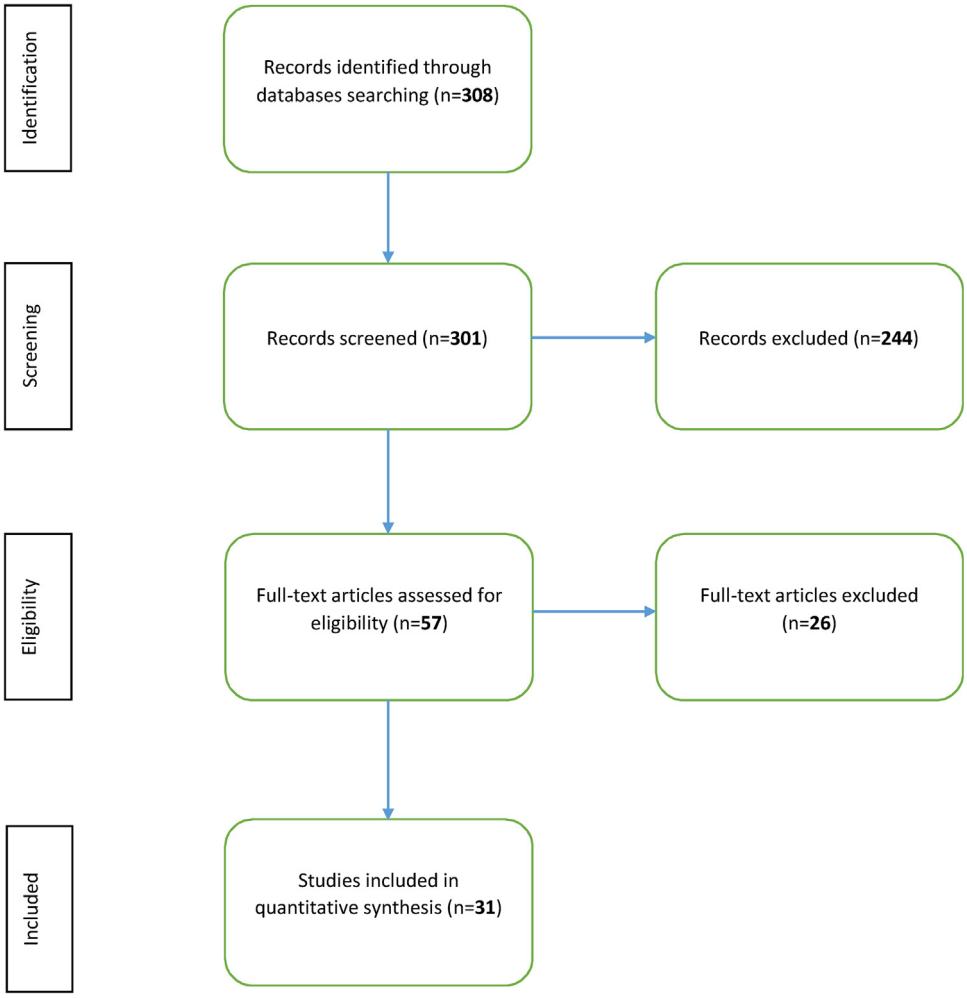


Fig. 2 – PRISMA flow diagram representing search strategy for the systematic review [39].

IV rt-PA). The second group included studies where patients were treated with intra-arterial thrombolysis, either alone or in combination with intravenous thrombolysis in any IV/IA rt-PA dose proportion (group 2: IV rt-PA ± IA rt-PA). The third group included studies in which patients were treated with mechanical thrombectomy, regardless of the device used, preceded or not with administration of rt-PA either IV or IA regardless of the dose (group 3: MT ± IA rt-PA ± IV rt-PA).

Taking into account the small number of studies in group 1, we expanded our analysis by combining groups 1 and 2 into one, thus comparing effects of any rt-PA treatment (either IV or IA or combined) with thrombectomy.

2.4. *Summary measures*

The main endpoint of this study was a 3-month mRS score, independent of other measures of the treatment, like recanalization or reperfusion. The favorable outcome was defined as mRS score 0–2 (patients functionally independent). We have also performed an extra meta-analysis for mortality (3-month survivors versus deaths). Percentages and 95% confidence intervals were estimated for each study, as was the overall effect.

2.5. *Statistical analysis*

To establish variance of individual studies, we applied the Freeman-Tukey double arcsine transformation. The meta-analysis was based on a random effects model, where we applied a combination of DerSimonian and Laird model with transformed proportions. Ultimately, overall effects were back-transformed. The 95% confidence intervals of the estimates were performed using the Wilson method with continuity correction. Heterogeneity was assessed using the I^2 statistic and Q test. Overall effects for a favorable outcome, as well as for mortality, were compared using the Q-test based on analysis of variance [38]. All analyses were performed using the meta package for R V3.2.3. The significance threshold was set at .05.

The possibility of publication bias was evaluated by visual analysis of a funnel plot, the Begg and Mazumdar's rank correlation test, and the Egger's linear regression.

2.6. *Comparison between the three therapeutic approaches*

We compared the functional outcome and mortality between each of the three therapeutic approaches (groups 1, 2, and 3)

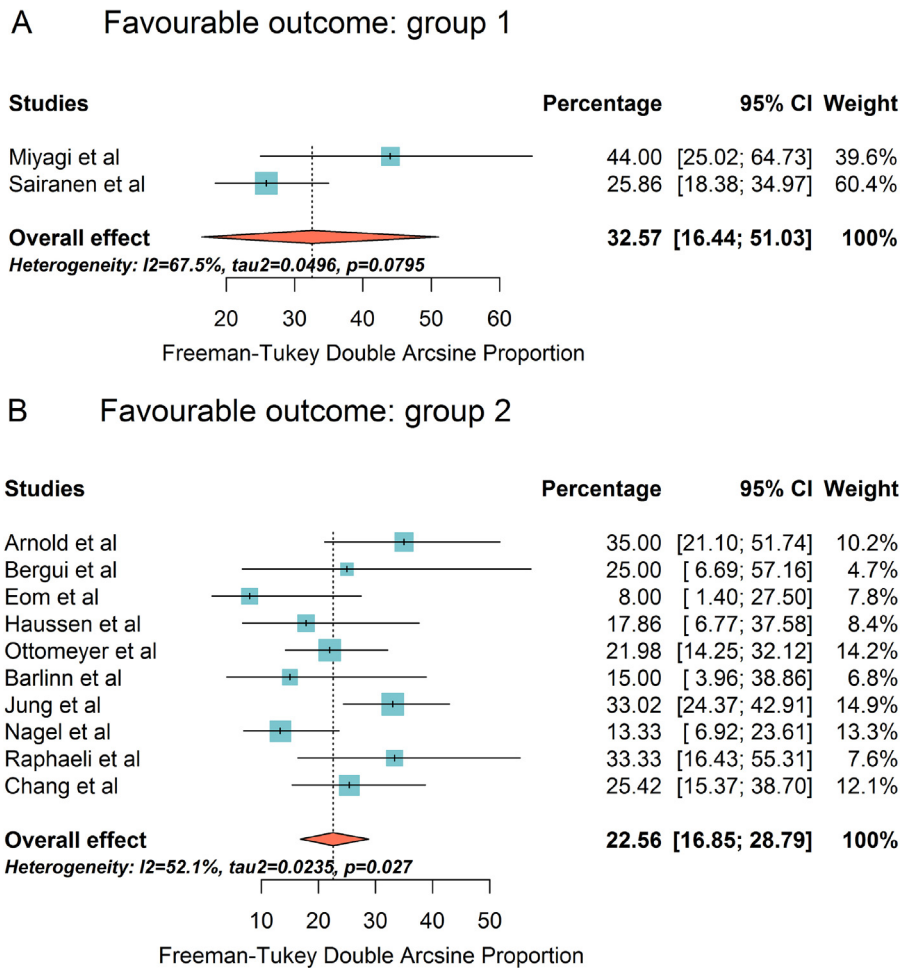


Fig. 3 – Forest plots for (a) favorable outcome in group 1; (b) favorable outcome in group 2; (c) favorable outcome in group 3; (d) mortality in group 1; (e) mortality in group 2; (f) mortality in group 3; (g) favorable outcome for groups 1 and 2 combined; and (h) mortality in group 1 and 2 combined.

using Q test subgroup analysis, based on analysis of variance. For this purpose, we assumed that the set of meta-analyses for the selected end-points (functional outcome, mortality) will constitute a set of the subgroups. This approach is commonly used in the subgroups analysis, although it does have some important limitations [38].

3. Results

3.1. Study characteristics

Application of the given criteria through the two databases resulted in identification of 308 records. Following elimination of duplicates (including different analyses – papers based on the same treated populations) and screening of the titles and abstracts, the list of articles shortened to 57 items. Full texts of the latter were carefully read by two independent authors, who finally selected 31 studies with 1358 subjects to be included in the review and meta-analyses (Fig. 2). MT devices used in the selected studies included Solitaire, Trevo, Catch, Phenox, Angio jet Ultra, ReVive, Penumbra.

Among the analyzed studies, nine were prospective single-center trials, fifteen were retrospective single-center trials, and the remaining six were retrospective multicenter studies. Characteristics of the included articles are shown in Tables 3–5.

3.2. Functional outcome and mortality

The weighted pooled estimates of the favorable outcome (mRS 0–2 at 3 months) were 32.57% (95% CI 16.44–51.03%/I^2 = 67.5%, p = 0.0795) in the first group, 22.56% (95% CI 16.85–28.79%/I^2 = 52.1%, p = 0.027) in the second group, and 37.04% (95% CI 32.27–41.92%/I^2 = 32%, p = 0.0895) for the third group (Fig. 3).

The mortality rates (mRS 6 at 3 months) were 25.00% (95% CI 4.80–53.03%/I^2 = 88.7%, p = 0.0001) in group 1, 42.79% (95% CI

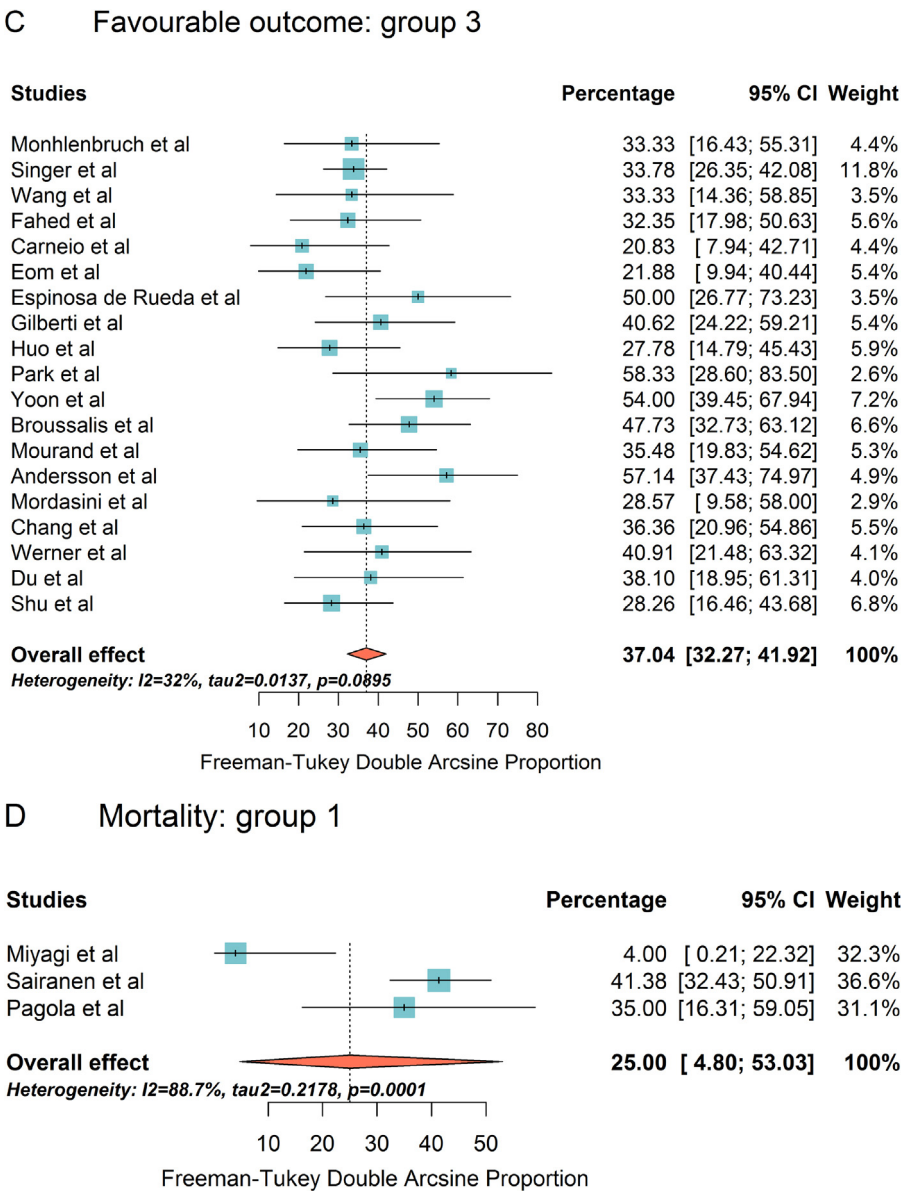


Fig. 3. (Continued).

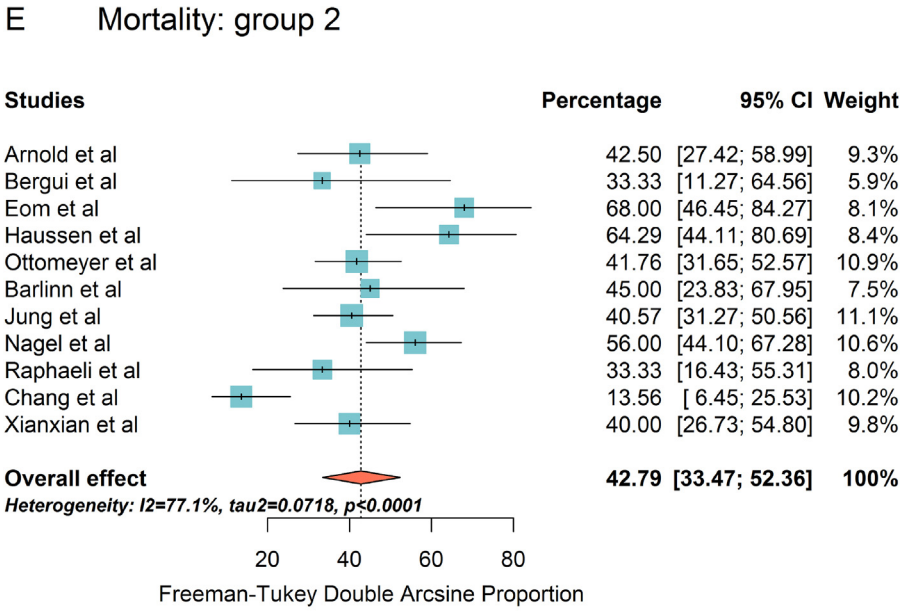
33.47–52.36%/I^2 = 77.1%, $p < 0.0001$) in group 2, and 24.50% (95% CI 19.24–30.13%/I^2 = 53.1%, $p = 0.0043$) for the third group (Fig. 3).

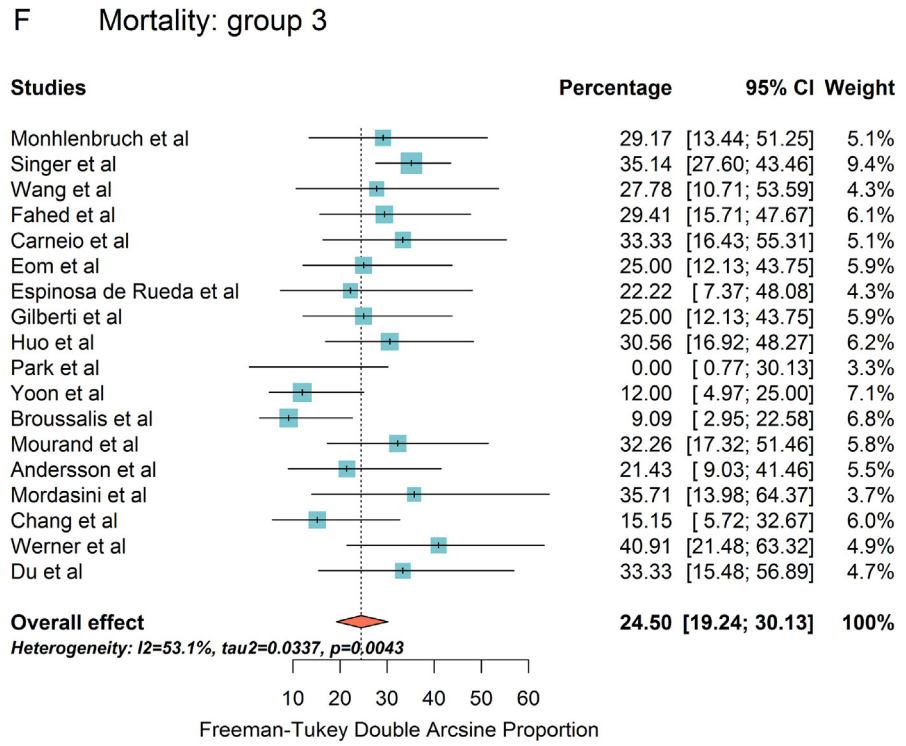
The Q-test subgroup analysis revealed the statistical superiority of the mechanical thrombectomy (MT ± IV rt-PA ± IA rt-PA: group 3) over IA rt-PA ± IV rt-PA (group 2) (mRS 0–2: $p = 0.0003$, mRS 6: $p = 0.0010$) and over any rt-PA administration (either IV rt-PA or IA rt-PA ± IV rt-PA: combined groups 1 + 2) (mRS 0–2: $p = 0.0006$, mRS 6: $p = 0.0056$) (Table 1). Current data on specific BAO treatment are insufficient to assess the superiority between MT (MT ± IV rt-PA ± IA rt-PA: group 3) and IV rt-PA (group 1) or between IA rt-PA ± IV rt-PA (group 2) and IV rt-PA (group 1) due to low number of reported patients in the latter (Table 1).

The weighted pooled estimate of a favorable outcome (mRS 0–2) for the effects of any rt-PA treatment (IA and/or IV; combined groups 1 and 2) was 24.18% (95% CI 18.95–29.80%/I^2 = 53%, $p = 0.0156$), whereas the mortality rate (mRS 6) was 39.09% (95% CI 30.50–48.01%/I^2 = 80%, $p < 0.0001$).

3.3. *Publication bias across studies*

We found no evidence of publication bias in the funnel plot, the Begg and Mazumdar's rank correlation test, and the Egger's





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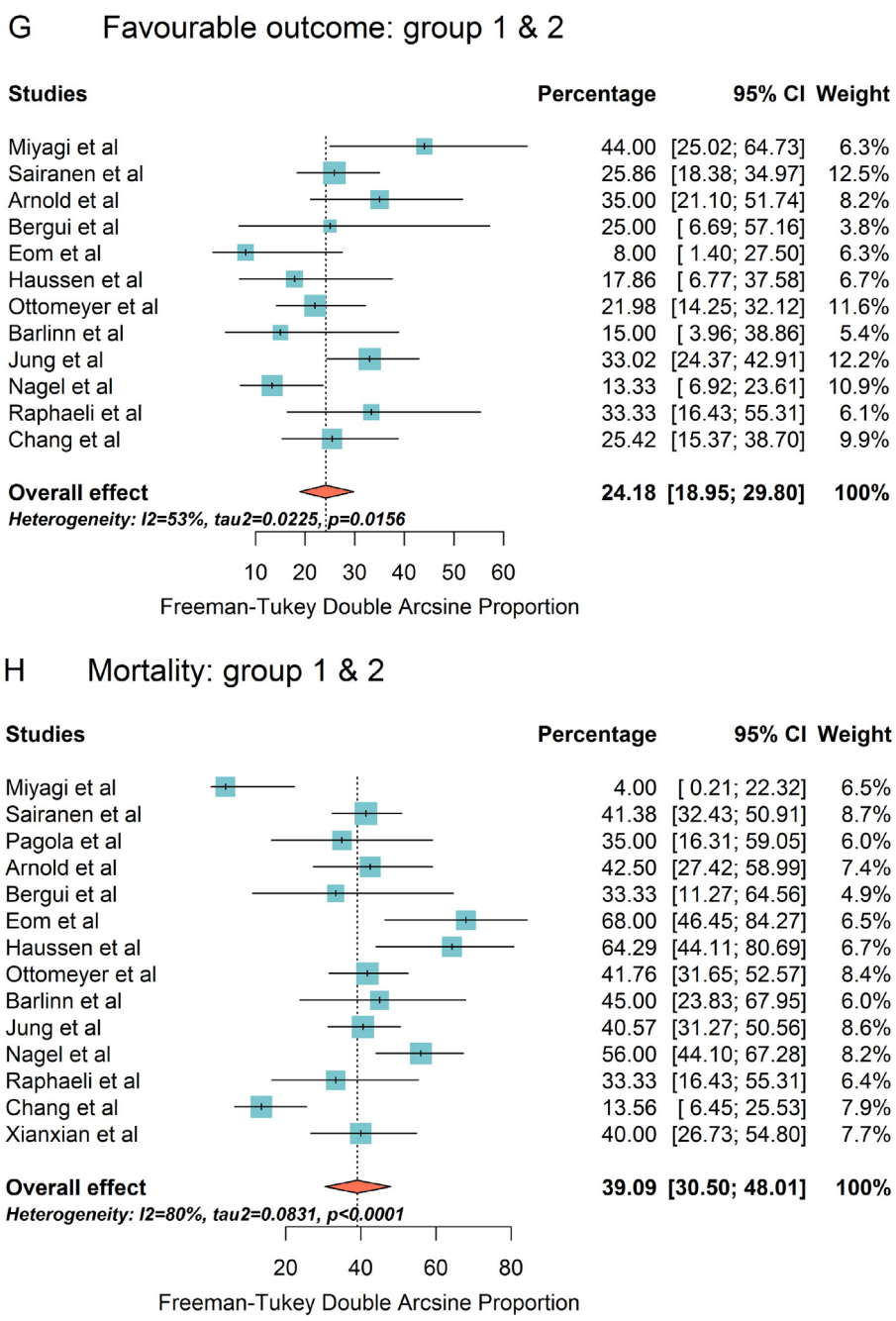

Fig. 3. (Continued).

linear regression analysis (Table 2). The overall evaluation of the risk of bias across studies is presented in Fig. 1. However, of note is that the number of studies in the first group (IV rt-PA) was insufficient to explore the bias across them.

4. Discussion

This is a first work showing meta-analyses for the functional outcome of all three basic methods of the treatment of BAO, followed by a comparison between these approaches.

The main end-point for the analysis was defined as mRS 0–2, and the secondary end-point was survival, both after 3 months, with no extra variables, such as Barthel's Index or Glasgow Outcome Scale, used in some studies.

Our systematic review revealed that current empirical and observational data on the effects of the three basic approaches of the treatment of acute BAO are insufficient to generate high-class evidence-based medicine guidelines. Among the records shortlisted for this meta-analysis, there was no single randomized clinical trial. Interestingly, manually the easiest and the most available IV rt-PA had the poorest empirical information, summing up to only 2 studies (when considering

Table 1 – Results of the Q-test (comparison between three therapeutic approaches).

Comparison	Q statistic	Degree of freedom (*df*)	P value
Favorable outcome groups 1 vs. 2 vs. 3	13.005	2	0.0015
Favorable outcome groups 1 vs. 2	1.136	1	0.2864
Favorable outcome groups 2 vs. 3	13.004	1	0.0003
Favorable outcome groups 1 vs. 3	0.239	1	0.6246
Mortality groups 1 vs. 2 vs. 3	10.992	2	0.0041
Mortality groups 1 vs. 2	1.452	1	0.2283
Mortality groups 2 vs. 3	10.869	1	0.0010
Mortality groups 1 vs. 3	0.0007	1	0.979
Favorable outcome groups 1 and 2 vs. 3	11.790	1	0.0006
Mortality groups 1 and 2 vs. 3	7.680	1	0.0056

Table 2 – Results of Begg and Mazumdar's test and Egger's test for groups 2–3.

Outcome	Begg and Mazumdar's test	Egger's test
Favorable outcome group 1	–	–
Favorable outcome group 2	$p = 0.5312$	$p = 0.6239$
Favorable outcome group 3	$p = 0.5281$	$p = 0.5588$
Favorable outcome group 1 and 2	$p = 0.7311$	$p = 0.8919$
Mortality group 1	–	–
Mortality group 2	$p = 0.6971$	$p = 0.6742$
Mortality group 3	$p = 0.5949$	$p = 0.3528$
Mortality group 1 and 2	$p = 0.7007$	$p = 0.7941$

Table 3 – Characteristics of studies included in group 1.

Reference	Study period	Study design	Patients (*n*)	Mean age (years)	Favorable outcome (mRS 0–2) (%)	Mortality (%)	Median time to therapy (h)
Miyagi et al. [2]	2005–2008	R, multicenter	25	70	44	4	2.5
Sairanen et al. [3][a]	1995–2008	P, single-center	116	63	26	41	8.7
Pagola et al. [4]	–	P, –	20	67	–	35	3

mRS – modified Rankin Scale score; P – prospective; R – retrospective.
[a] 7/116-I-A.

mRS) [2,3] or 3 (when considering mortality) [2–4]. The studies were both retrospective and prospective, with a relatively small number of patients in each group, which carries a risk of publication bias and might overestimate outcome effects.

Despite those preliminary limitations, this analysis carries useful information. The percentage of favorable-outcome patients after IV rt-PA was 32.57%, whereas following IA rt-PA (preceded or not by IV rt-PA), it was 22.56%. In a former meta-analysis by Lindsberg and Mattle [36], application of thrombolysis, either intravenous or intra-arterial, had comparable results regarding good outcome (22% and 24%, respectively) and obviously differed to the numbers revealed in our meta-analysis, mainly due to fewer studies being taken into account and different methodological approaches.

These current data provide a higher class of evidence for the superiority of the use of endovascular mechanical devices. The mechanical thrombectomy with the use of any endovascular device, preceded or not by any rt-PA administration, is the most efficient therapeutic method for this condition if measured by functional outcome and mortality. In our meta-analysis, this approach was better than two others (separately or combined), reaching the highest pooled estimate of favorable outcome and the lowest mortality rate.

The Q-test subgroup analysis revealed that the mechanical thrombectomy in BAO preceded or not by rt-PA administration (group 3) is superior to IA rt-PA preceded or not by IV rt-PA (group 2) and to any rt-PA administration (either IV rt-PA or IA rt-PA: combined groups 1 + 2). However, this analytical method, although frequently used for similar comparisons, has some limitations and must be treated with caution [38].

Previous systematic reviews [33–35] have also demonstrated lower rates of mortality and higher likelihood of favorable outcome in acute BAO when mechanical thrombectomy was applied.

There are several basic variables that might influence the results of the effect of each of the therapeutic approaches. For example, IV rt-PA, IA rt-PA, and MT might have different efficiencies in different time windows after stroke. However, the authors assessing full texts of the papers (eligibility step of the systematic review) did not find sufficient data regarding the time from stroke onset to therapeutic intervention to be able to take them into account in the meta-analyses.

Table 4 – Characteristics of studies included in group 2.

Reference	Study period	Study design	Patients (*n*)	Mean age (years)	Favorable outcome (mRS 0–2) (%)	Mortality (%)	Median time to therapy (h)
Arnold et al. [5]	1992–2002	R, multicenter	40	58	35	43	5.5[a]
Bergui et al. [6]	2003–2004	P, single-center	12	64	25	33	7
Eom et al. [7]	2006–2013	R, multicenter	25	67	8	68	5
Haussen et al. [8]	2007–2012	R, multicenter	28	64	18	64	7
Ottomeyer et al. [9][b]	2002–2009	R, single-center	91	63	22	42	6.6[a]
Barlinn et al. [10]	2002–2007	P, single-center	20	62	15	45	5
Jung et al. [11]	1992–2010	P, single-center	106	62	33	41	5.5
Nagel et al. [12]	1998–2006	P, single-center	75	68	13	56	5
Raphaeli et al. [13]	–	R, single-center	24	55	33	33	–
Chang et al. [14]	2007–2014	R, single-center	59	70	25	14	–
Xianxian et al. [15]	–	R, single-center	50	–	–	40	–

mRS – modified Rankin Scale score; P – prospective; R – retrospective.
[a] Mean.
[b] 9/91-IV.

Table 5 – Characteristics of studies included in group 3.

Reference	Study period	Study design	Patients (*n*)	Mean age (year)	Favorable outcome (mRS 0–2) (%)	Mortality (%)	Median time to therapy (h)
Monhlenbruch et al. [16]	2009–2012	P, single-center	24	70[b]	33	29	4.2
Singer et al. [17]	2011–2013	R, multicenter	148	71[b]	34	35	–
Wang et al. [18]	2011–2013	R, single-center	18	60	33	28	3.2
Fahed et al. [19]	2006–2015	R, single-center	34	62	32	29	–
Carneiro et al. [20]	2012–2014	R, single-center	24	57	21	33	–
Eom et al. [7]	2006–2013	R, multicenter	32	68	22	25	4.7[a]
Espinosa de Rueda et al. [21]	2010–2012	R, single-center	18	68	50	22	6.1[a]
Gilberti et al. [22]	2010–2015	R, single-center	32	64	41	25	7.7[a]
Huo et al. [23]	2012–2015	P, single-center	36	59	28	31	7.5
Park et al. [24]	2013–2015	R, single-center	12	64	58	0	6
Yoon et al. [25]	2010–2015	R, single-center	50	71[b]	54	12	4.6
Broussalis et al. [26]	2005–2012	P, single-center	44	68	48	9	4
Mourand et al. [27]	2009–2011	P, single-center	31	61	35	32	6
Andersson et al. [28]	2005–2010	R, single-center	28	–	57	21	–
Mordasini et al. [29]	2010–2011	R, single-center	14	65[b]	29	36	6.9
Chang et al. [14]	2007–2014	R, single-center	33	–	36	15	–
Werner et al. [30]	2008–2013	R, single-center	22	60[b]	41	41	4.3
Du et al. [31]	2011–2014	R, single-center	21	58	38	33	–
Shu et al. [32]	2007–2015	R, single-center	46	–	28	–	–

mRS – modified Rankin Scales score; P – prospective; R – retrospective.
[a] Mean.
[b] Median.

Another limitation of our approach is the division of the therapies into three groups only. The ''bridging therapy'' (application of IV rt-PA prior to IA rt-PA or any or both of the two prior to MT), and the MT device construction, might influence the outcome, which was intentionally ignored in this analysis to obtain more reliable (including larger groups) data for the statistical workout. Finally, there are a lot of other factors ignored in the analyzed studies that might influence outcome after stroke such as for example blood pressure values in the early phase [40], brain and body temperatures [41–43], or various metabolic conditions and genetic variants [44].

In conclusion, the stent-retriever mechanical thrombectomy seems to be the most effective method of treatment of BAO, showing a good safety profile. The efficacy of intravenous thrombolytic therapy remains unclear among others due to the insufficient number of studies and high heterogeneity across studies. Randomized controlled trials or large high-class observational studies are required to deliver unbiased data about the treatment of patients with basilar artery occlusion.

Conflict of interest

None declared.

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None declared.

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