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Review

Mothership versus Drip-and-Ship Model for Mechanical Thrombectomy in Acute Stroke: A Systematic Review and Meta-Analysis for Clinical and Radiological Outcomes

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Background and Purpose Substantial uncertainty exists on the benefit of organizational paradigms in stroke networks. Here we systematically reviewed and meta-analyzed data from studies comparing functional outcome between the mothership (MS) and the drip and ship (DS) models.

Methods The meta-analysis protocol was registered international prospective register of systematic reviews (PROSPERO) and followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PubMed, EMBASE, and Cochrane Central databases were searched for randomized-controlled clinical trials (RCTs), retrospective and prospective studies comparing MS versus DS. Primary endpoints were functional independence at 90 days (modified Rankin Scale <3) and successful recanalization (Thrombolysis in Cerebral Infarction Scale [TICI] >2a); secondary endpoints were 3-month mortality and symptomatic intracranial haemorrhage (sICH). Odds ratios for endpoints were pooled using the random effects model and were compared between the two organizational models.

Results Overall, 18 studies (n=7,017) were included in quantitative synthesis. MS paradigm was superior to DS model for functional independence (odds ratio, 1.34; 95% confidence interval, 1.16 to 1.55; I^2=30%). Meta-regression analysis revealed association between onset-to-needle time and good functional outcome, with longer onset-to-needle time being detrimental. Similar rates of recanalization, sICH and mortality at 90 days were documented between MS and DS.

Conclusions Patients with acute ischemic stroke eligible for reperfusion strategies might benefit more from MS paradigm as compared to DS. RCTs are needed to further refine best management taking into account logistics, facilities and resources.

Keywords Stroke; Mothership; Drip and ship; Thrombectomy; Endovascular procedures

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Introduction

Previous randomized-controlled clinical trials (RCTs) showed that the combination of intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT) is effective in patients with ischemic stroke due to a large vessel occlusion.[1-3] Current international guidelines have been updated accordingly.[4] However, EVT is only available at Comprehensive Stroke Centers (CSC), which are fewer than Primary Stroke Centers (PSC), the latter being only able to administer IVT. Therefore, two main organizational paradigms have been developed: the mothership (MS), in which the patient is directly brought to the CSC, and the drip and ship (DS) model, where initially assessment and eventual IVT at the PSC are followed by "shipping" to the CSC. The choice of a model over another implies clinical consequences for treated patients as well as for local health policies, including the distribution of hospital facilities over the region of interest.

Previous systematic reviews comparing MS versus DS models were limited to few studies and provided conflicting results.[5,6] Computational modeling provided potential insights on time of transport, although with consistent limitations due to assumptions of treatment efficacy and patient eligibility.[7] Therefore, no conclusive evidence is available to date concerning the superiority of one model over the other by clinical and economic results.

We conducted a systematic review and pooled data meta-analysis of studies comparing MS versus DS model, including subgroup analysis by type of treatment, clinical severity and timing of treatments.

Methods

Search strategy

The methods and guidelines of this study-level meta-analysis followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[8] and study protocol registered with PROSPERO (CRD42019135915). Two reviewers systematically searched Pubmed, EMBASE and Cochrane Central register of Controlled Trials databases for studies comparing MS versus DS published between January 1990 and February 1st, 2020. Search strategy was based on combination of terms, including "mothership," "drip and ship," "organization model," "stroke," "thrombolysis," "thrombectomy," as either keywords or MeSH terms. Reference lists and citing articles were also reviewed to increase the identification of relevant studies.

Selection criteria

We included RCTs, prospective and retrospective studies reporting the clinical efficacy and safety of MS or DS model among adult (≥18) patients with acute ischemic stroke, independently from the device used. We limited the studies to English language and excluded case reports, small case series (<20), conference proceedings and reviews. The interventional group comprised patients treated in a MS model, while the control group was represented by the DS paradigm.

Endpoints

The primary endpoint was functional independence at 90 days from stroke onset, defined as modified Rankin Scale score <3. Secondary endpoints were (1) rate of good recanalization according to Thrombolysis in Cerebral Infarction Scale (TICI) grade (2b or 3), (2) mortality at 90 days from stroke onset, (3) and the occurrence of symptomatic intracerebral haemorrhage (sICH), according to the definition of individual studies.

Data extraction and bias assessment

Two reviewers independently extracted data concerning baseline and outcome characteristics of each included study, as well as its methodological design. We reported the lack of data on outcome, when appropriate. Risk of bias was assessed and reported according to the recommendations of the Cochrane Handbook for Systematic Reviews of Intervention, applying the Cochrane risk of bias tool or the Newcastle-Ottawa Scale for bias assessment when appropriate. Funnel plots were implemented for publication bias.

Statistical analysis

We performed a statistical analysis pooling data in the intervention group and the control group. Outcome heterogeneity was evaluated with Cochrane's Q test I^2. We calculated odds ratio (ORs) and 95% confidence intervals (CIs), with a random effects model, for all outcomes. We calculated I^2 statistics, and heterogeneity was classified as moderate (I^2 30% to 50%), substantial (I^2 50% to 75%), or considerable (I^2 75% to 100%). If the results were heterogenous, we planned to use sensitivity analysis to investigate how the results differed when we excluded studies with highest risk of bias. Subgroup analysis for the primary outcome was predefined for different types of treatment, including studies considering bridging therapy only. Sensitivity analysis through leave-one out paradigm was used to test robustness of the findings. We report the analysis results graphically using forest plots for outcomes of single included trials and the total treatment effects. We also calculated the number needed to treat (NNT) for the primary endpoint using the formula NNT=1/[(1−RR)×mortality rate in control group]. Finally, we introduced covariates to reduce heterogene-

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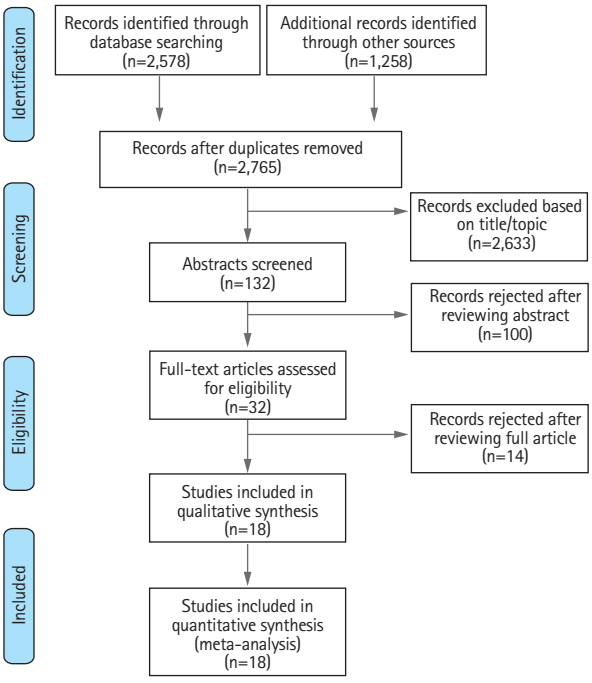

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow-chart for selection of studies included in the meta-analysis.

ity of meta-analysis and we performed a meta-regression analysis to detect the influence of these variables on the primary endpoint. In particular, we considered the differences of means between interventional and control groups of each included study concerning age, clinical severity summarized by the score of National Institutes of Health Stroke Scale (NIHSS), onset-to-groin time (OGT) and onset-to-needle time (ONT). We reported graphical representation of final results by bubble-plots. Data analysis was performed using Review Manager version 5.3 (The Cochrane Collaboration 2012, Copenhagen, Denmark) and R software version 3.3.1 (packages metaphor,[9] meta; R Foundation for Statistical Computing, Vienna, Austria).

Results

Systematic search retrieved 18 studies including 7,017 patients (PRISMA flowchart) (Figure 1).[10-27] Most of the included studies were observational and prospective, only one study was a RCT[15] (Table 1). As a result, quality of studies ranged fair to good, with only one RCT achieving optimal score on risk of bias assessment. Funnel plot showed low levels of visual asymmetry (Supplementary Figure 1 for complete bias assessment). No significant differences emerged comparing patients treated in

Table 1. Summary of included studies

Study	Age (yr)	Sample			NIHSS	ONT (min)		OGT (min)		No. of IVT (%)	
		Total	Mothership	Drip & Ship		Mothership	Drip & Ship	Mothership	Drip & Ship	Mothership	Drip & Ship
Adams et al. (2019)[10]	72	214	124	90	16	NA	NA	131	248	52 (42)	49 (54)
Cappelen-Smith et al. (2016)[19]	67	33	20	13	21	NA	NA	NA	NA	7 (35)	9 (69)
Feil et al. (2020)[11]	71	410	221	189	16	95	95	152	256	255 (overall)	
Froehler et al. (2017)[17]	68	906	498	408	17	89	98	137	237	329 (66)	299 (73)
Gerschenfeld et al. (2017)[21]	72	159	59	100	16	135	150	189	248	59 (100)	100 (100)
Hiyama et al. (2016)[22]	75	45	12	33	20	NA	NA	166	189	12 (100)	33 (100)
Jayaraman et al. (2020)[12]	76	232	88	144	18	50*	62*	93	152	48 (55)	94 (65)
Kim et al. (2016)[18]	67	820	678	142	9	110	161	NA	NA	678 (100)	142 (100)
Mourand et al. (2019)[14]	69	179	93	86	18	165	152	215	315	48 (52)	70 (81)
Park et al. (2016)[23]	69	105	77	28	12	NA	NA	219	300	77 (100)	28 (100)
Park et al. (2016)[24]	68	1,898	1,599	299	11	113†	120†	200	305	1,599 (100)	299 (100)
Pfaff et al. (2017)[16]	65	112	74	38	19	NA	NA	178	283	54 (73)	29 (76)
Prothmann et al. (2017)[26]	68	87	37	50	15	NA	NA	137	233	23 (62)	35 (70)
Rinaldo et al. (2017)[25]	66	140	62	78	18	NA	NA	277	420	40 (65)	42 (54)
Saver et al. (2015)[15]	65	98	67	31	NA	NA	NA	275	180	NA	NA
van Veenendaal et al. (2018)[27]	70	178	50	128	17	NA	NA	158	293	32 (64)	97 (76)
Weber et al. (2016)[20]	71	643	300	343	15	92‡	115‡	150	233	NA	NA
Weisenburger-Lile et al. (2019)[13]	67	971	298	673	16	131	150	171	260	298 (100)	673 (100)

NIHSS, National Institutes of Health Stroke Scale; ONT, onset-to-needle time; OGT, onset-to-groin time; IVT, intravenous thrombolysis; NA, not available.
*Onset time replaced by scene departure; †Includes patients treated with bridging; ‡Data for whole cohort, including patients lost to follow-up.

Table 2. Differences between groups

Variable	Mothership (n=4,338)	Drip & Ship (n=2,808)	*P*
Male sex (%)	56	55	0.406
Age (yr)	69.6±11.0	69.1±11.0	0.065
NIHSS score at admission	15.7±5.0	15.6±5.0	0.409
ONT (min)	120±27	132±27	0.006
OGT (min)	179±49	276±124	<0.001
IVT rate (%)	3,356 (89)	1,999 (87)	0.462
Recanalization rate (%)	1,574 (79)	1,774 (79)	0.705

Values are presented as mean±standard deviation or number (%).
NIHSS, National Institutes of Health Stroke Scale; ONT, onset-to-needle time; OGT, onset-to-groin time; IVT, intravenous thrombolysis.

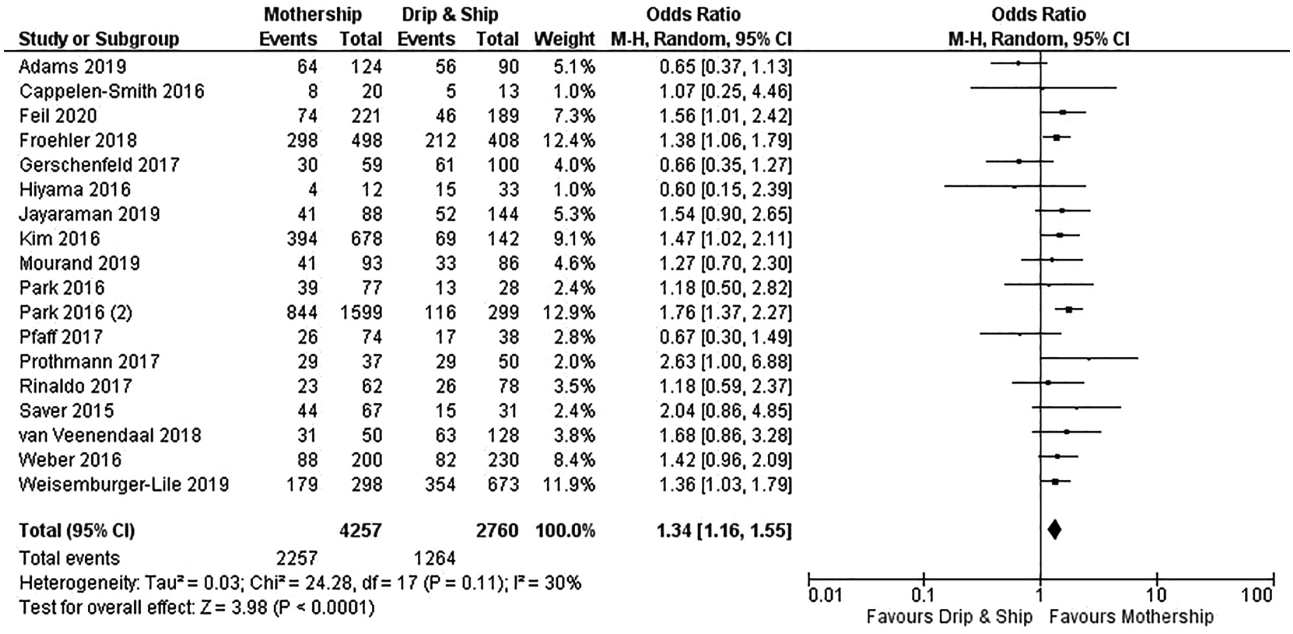

Figure 2. Forest plot showing the association of organizational paradigms with functional independence (modified Rankin Scale 0–2) at 3 months. M-H, Mantel-Haenszel; CI, confidence interval.

the two organizational paradigms for sex, age, and NIHSS score at admission. On the contrary, DS patients had longer onset-to-treatment timing (Table 2).

Considering the primary endpoint of functional independence at 90 days, MS paradigm was superior to DS model (OR, 1.34; 95% CI, 1.16 to 1.55; I^2=30%) (Figure 2). More specifically, the rates of functional independence were 53% and 47% in the MS and DS organizational paradigms respectively, with a NNT of 29 in favor of MS model (Figure 2). Results from DerSimonian & Laird model were also confirmed applying the Hartung-Knapp-Sidik-Jonkman model (OR, 1.38; 95% CI, 1.20 to 1.59; $P_{heterogeneity}$=0.11). In the subgroup analysis restricted to studies exploring bridging therapy, the MS model provided marginally higher rate of functional independence (OR, 1.26; 95% CI, 0.98 to 1.63; I^2=34%) (Figure 3).

Meta-regression analysis revealed a significant association between ONT and good functional outcome, with longer ONT being detrimental for recovery (Supplementary Figure 2). Differences of age, clinical severity at presentation, and OGT between study groups did not have significant correlation with functional outcome (Supplementary Figures 3-5).

MS and DS had similar rates of mortality at 90 days (OR, 0.94; 95% CI, 0.78 to 1.13; I^2=28%) and successful recanalization (OR, 0.81; 95% CI, 0.54 to 1.21; I^2=80%) (Supplementary

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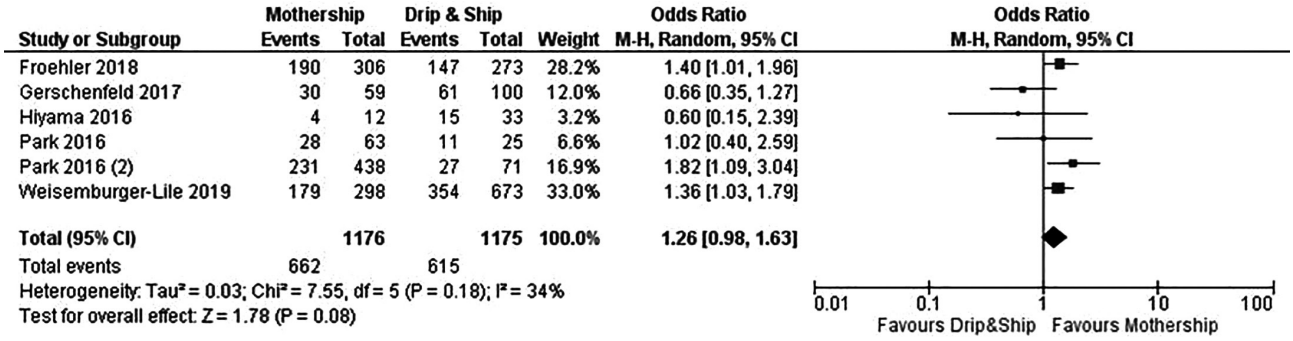


Figure 3. Forest plot showing the association of organizational paradigms with functional independence (modified Rankin Scale 0–2) at 3 months in subgroup of patients treated with bridging therapy (combination of intravenous thrombolysis and endovascular thrombectomy). M-H, Mantel-Haenszel; CI, confidence interval.

Figures 6 and 7). Sensitivity analysis through leave-one out paradigm confirmed results (Supplementary Table 1). Pooling data from all observational studies, excluding RCT, MS was still superior to DS paradigm 1.33 (95% CI, 1.16 to 1.53) (Supplementary Table 1). Combinatorial analysis further confirmed clustering of possible pooled estimates in favor of MS for primary outcome (Supplementary Figure 8).

Overall, no significant difference was noted in terms of sICH depending on organizational paradigm, with a 6.3% and 6.7% in MS and DS models respectively (OR, 0.87; 95% CI, 0.70 to 1.10; I^2=15%) (Supplementary Figure 9). There was substantial heterogeneity for the endpoint of successful recanalization across the included studies (*P* for Cochran Q <0.00001, I^2=80%). There was little or no heterogeneity regarding all the other endpoints.

Discussion

In this systematic review and meta-analysis including patients with acute ischemic stroke eligible for reperfusion strategies, MS organizational paradigm was associated with a higher rates of functional independence at 3 months compared to DS. Our findings add and put into context previous studies and systematic reviews,[5,6,28] particularly regarding the role of treatment timing on plausible benefit. MS provided better 90-day outcome compared to DS in a previous meta-analysis, which however was limited to eight studies (n=2,068) and provided no meta-regression for timing of treatment.[5] MS superiority failed to be replicated in a meta-analysis integrating 9 studies (n=4,127), which showed similar performance of the two paradigms.[6] Reviews put into question MS superiority,[28] and previous conditional modeling providing suggestions for network organization was consistently limited by assumptions on eligibility, door-to-needle time at PSCs, and standardized rates of recanalization.[7,29] Our results, deriving from 18 studies (n>7,000), provide substantial insights in the overall net benefit of MS compared to DS, and detail effects on both good functional outcome, sICH and mortality. Specific, patients treated under MS paradigm had approximately 40% higher odds of being functionally independent at 3 months, with no increase in the risk of sICH, or mortality. The benefit of MS on functional outcome was further confirmed across sensitivity analysis. Therefore, MS might be preferred to DS whenever local facilities allow the application of this organizational paradigm.

A marginal and non-significant benefit of MS over DS was also found taking into account studies investigating bridging. This finding needs to be looked at with caution. First, the analysis was consistently limited by the sample size and heterogeneity, with large-sample studies clustering towards MS benefit versus small-sample ones distributing in the opposite direction. Second, the fact that such trend emerges together with the lack of relationship between OGT and functional outcome might suggest that what happens before EVT translates on outcome. To this extent, ONT was correlated with functional outcome, and was significantly shorter in MS group, suggesting that the rapid access to reperfusion strategies still represents the principal target to achieve good outcome. Results from this meta-analysis highlight that longer ONT negatively impacted 3-month functional outcome, suggesting that logistics should be appropriately addressed when configuring a stroke network. The fact that age and clinical severity did not impact on the benefit of paradigm choice on functional outcomes argues in favor of common pathways for all stroke patients, independently from age and clinical severity at stroke onset.

Regarding recanalization, a marginal, although not significant, increase in rates of recanalization with DS was found

compared to MS with substantial heterogeneity detected across included studies. These findings support similar efficacy of the two organizational paradigms, although it might also prompt speculations on possible higher rates of futile recanalization in patients managed via DS, which might be attributable to long transportation-time between primary and comprehensive centers, treatment in late time-windows, and lack of eligibility rechecking at arrival.

Limitations to this meta-analysis might be related to the design of included studies, as well as in the use of tabular data, which precluded further adjustment for confounding factors. Second, our results might not be fully representative of stroke care in the near future, when expansion of tissue-based windows for treatment might consistently refine the advantages of one paradigm over the other. To this extent, implementation of simulation modeling might represent a useful resource to orientate logistics, with appropriate continuous audit/feedback.[7] Third, meta-regression analysis was performed with the caveat of low number of studies, and therefore results regarding ONT timing should be considered with caution. Finally, meta-analysis did not include geographical factors and different centers performance, which might indeed represent critical details to organize the stroke network. However, given MS associates with improved functional outcome, policies might be implemented to support such paradigm in areas with transportation time to CSC below 45 minutes. The ongoing Transfer to the Local Stroke Center versus Direct Transfer to Endovascular Center of Acute Stroke Patients with Suspected Large Vessel Occlusion in the Catalan Territory (RACECAT; NCT02795962) and PREhospital Routage of Acute STroke Patients With Suspected Large Vessel Occlusion: Mothership Versus Drip and Ship (PRESTO-F; NCT04121013) trials will provide more answers to the open questions comparing MS and DS.

Conclusions

Patients with acute ischemic stroke eligible for reperfusion strategies might benefit from MS paradigm compared to DS. RCTs are needed to further refine best management taking into account logistics, facilities and resources.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2020.01767.

Disclosure

The authors have no financial conflicts of interest.

References

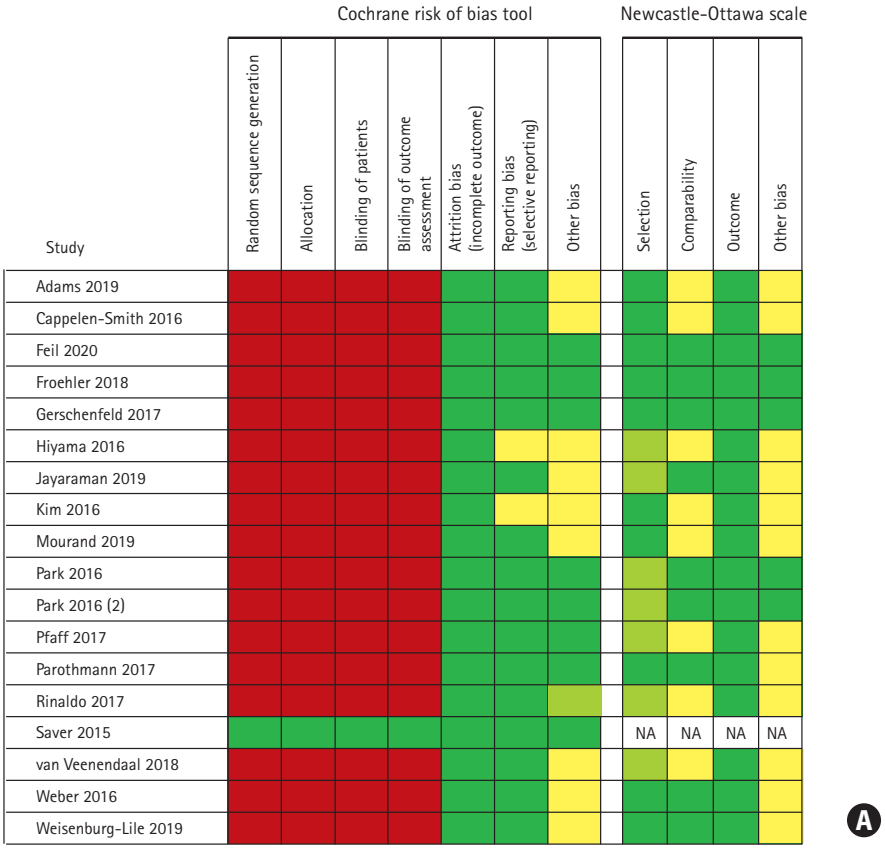
1. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet* 2016;387:1723-1731.
2. Vidale S, Agostoni E. Endovascular treatment of ischemic stroke: an updated meta-analysis of efficacy and safety. *Vasc Endovascular Surg* 2017;51:215-219.
3. Vidale S, Romoli M, Consoli D, Agostoni EC. Bridging versus direct mechanical thrombectomy in acute ischemic stroke: a subgroup pooled meta-analysis for time of intervention, eligibility, and study design. *Cerebrovasc Dis* 2020;49:223-232.
4. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2018;49:e46-e110.
5. Ismail M, Armoiry X, Tau N, Zhu F, Sadeh-Gonik U, Piotin M, et al. Mothership versus drip and ship for thrombectomy in patients who had an acute stroke: a systematic review and meta-analysis. *J Neurointerv Surg* 2019;11:14-19.
6. Ciccone A, Berge E, Fischer U. Systematic review of organizational models for intra-arterial treatment of acute ischemic stroke. *Int J Stroke* 2019;14:12-22.
7. Holodinsky JK, Williamson TS, Demchuk AM, Zhao H, Zhu L, Francis MJ, et al. Modeling stroke patient transport for all patients with suspected large-vessel occlusion. *JAMA Neurol* 2018;75:1477-1486.
8. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
9. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw* 2010;36:1-48.
10. Adams KM, Burns PA, Hunter A, Rennie I, Flynn PA, Smyth G, et al. Outcomes after thrombectomy in belfast: mothership and drip-and-ship in the real world. *Cerebrovasc Dis* 2019;47:231-237.
11. Feil K, Rémi J, Küpper C, Herzberg M, Dorn F, Kunz WG, et al. Drip and ship for mechanical thrombectomy within the Neurovascular Network of Southwest Bavaria. *Neurology* 2020;94:e453-e463.

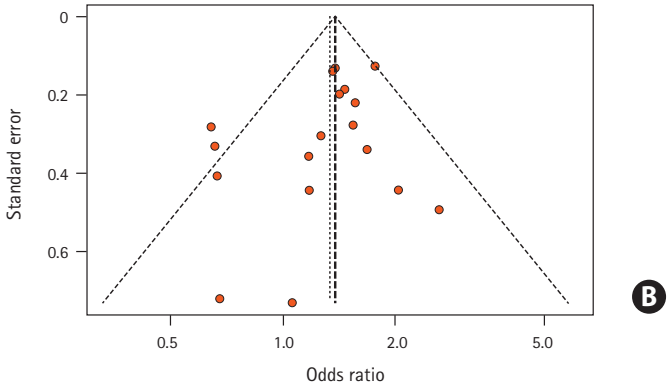
12. Jayaraman MV, Hemendinger ML, Baird GL, Yaghi S, Cutting S, Saad A, et al. Field triage for endovascular stroke therapy: a population-based comparison. *J Neurointerv Surg* 2020;12:233-239.
13. Weisenburger-Lile D, Blanc R, Kyheng M, Desilles JP, Labreuche J, Piotin M, et al. Direct admission versus secondary transfer for acute stroke patients treated with intravenous thrombolysis and thrombectomy: insights from the endovascular treatment in ischemic stroke registry. *Cerebrovasc Dis* 2019;47:112-120.
14. Mourand I, Malissart P, Dargazanli C, Nogue E, Bouly S, Gaillard N, et al. A regional network organization for thrombectomy for acute ischemic stroke in the anterior circulation; timing, safety, and effectiveness. *J Stroke Cerebrovasc Dis* 2019;28:259-266.
15. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med* 2015;372:2285-2295.
16. Pfaff J, Pham M, Herweh C, Wolf M, Ringleb PA, Schönenberger S, et al. Clinical outcome after mechanical thrombectomy in non-elderly patients with acute ischemic stroke in the anterior circulation: primary admission versus patients referred from remote hospitals. *Clin Neuroradiol* 2017;27:185-192.
17. Froehler MT, Saver JL, Zaidat OO, Jahan R, Aziz-Sultan MA, Klucznik RP, et al. Interhospital transfer before thrombectomy is associated with delayed treatment and worse outcome in the STRATIS registry (systematic evaluation of patients treated with neurothrombectomy devices for acute ischemic stroke). *Circulation* 2017;136:2311-2321.
18. Kim DH, Bae HJ, Han MK, Kim BJ, Park SS, Park TH, et al. Direct admission to stroke centers reduces treatment delay and improves clinical outcome after intravenous thrombolysis. *J Clin Neurosci* 2016;27:74-79.
19. Cappelen-Smith C, Cordato D, Calic Z, Cheung A, Wenderoth J. Endovascular thrombectomy for acute ischaemic stroke: a real-world experience. *Intern Med J* 2016;46:1038-1043.
20. Weber R, Reimann G, Weimar C, Winkler A, Berger K, Nordmeyer H, et al. Outcome and periprocedural time management in referred versus directly admitted stroke patients treated with thrombectomy. *Ther Adv Neurol Disord* 2016;9:79-84.
21. Gerschenfeld G, Muresan IP, Blanc R, Obadia M, Abrivard M, Piotin M, et al. Two paradigms for endovascular thrombectomy after intravenous thrombolysis for acute ischemic stroke. *JAMA Neurol* 2017;74:549-556.
22. Hiyama N, Yoshimura S, Shirakawa M, Uchida K, Oki Y, Shindo S, et al. Safety and effectiveness of drip, ship, and retrieve paradigm for acute ischemic stroke: a single center experience. *Neurol Med Chir (Tokyo)* 2016;56:731-736.
23. Park MS, Yoon W, Kim JT, Choi KH, Kang SH, Kim BC, et al. Drip, ship, and on-demand endovascular therapy for acute ischemic stroke. *PLoS One* 2016;11:e0150668.
24. Park MS, Lee JS, Park TH, Cho YJ, Hong KS, Park JM, et al. Characteristics of the drip-and-ship paradigm for patients with acute ischemic stroke in South Korea. *J Stroke Cerebrovasc Dis* 2016;25:2678-2687.
25. Rinaldo L, Brinjikji W, McCutcheon BA, Bydon M, Cloft H, Kallmes DF, et al. Hospital transfer associated with increased mortality after endovascular revascularization for acute ischemic stroke. *J Neurointerv Surg* 2017;9:1166-1172.
26. Prothmann S, Schwaiger BJ, Gersing AS, Reith W, Niederstadt T, Felber A, et al. Acute Recanalization of Thrombo-Embolic Ischemic Stroke with pREset (ARTESp): the impact of occlusion time on clinical outcome of directly admitted and transferred patients. *J Neurointerv Surg* 2017;9:817-822.
27. Van Veenendaal P, Yan B, Churilov L, Dowling R, Bush S, Mitchell P. Endovascular clot retrieval by hub-and-spoke service delivery is feasible compared with direct-to-mothership. *Cerebrovasc Dis* 2018;46:172-177.
28. Détraz L, Ernst M, Bourcier R. Stroke transfer and its organizational paradigm: review of organizational paradigms and the impact on outcome. *Clin Neuroradiol* 2018;28:473-480.
29. Holodinsky JK, Williamson TS, Kamal N, Mayank D, Hill MD, Goyal M. Drip and ship versus direct to comprehensive stroke center: conditional probability modeling. *Stroke* 2017;48:233-238.

Supplementary material

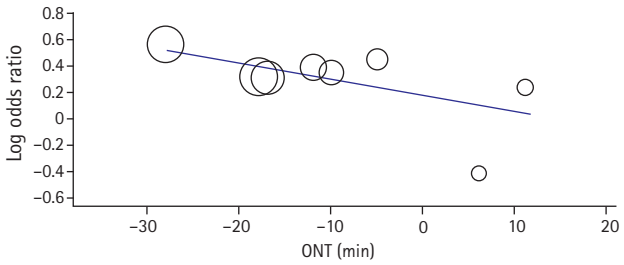
Boolean syntax for literature search in PubMed database

(((mothership[title/abstract]) OR (MS[title/abstract])) OR ((drip and ship[title/abstract]) OR (DS[title/abstract])) OR (hub and spoke[title/abstract])) AND (stroke[title/abstract] OR (cerebrovascular disease*[title/abstract]))

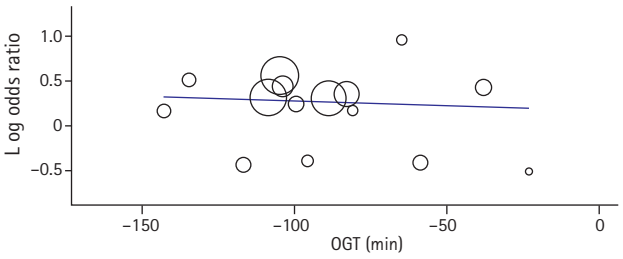




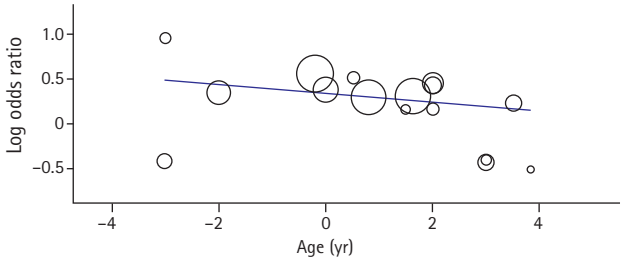
Supplementary Figure 1. Risk of bias summary (A) and publication bias Funnel plot (B). Color-based legend: red=high risk of bias, yellow=mild risk of bias, light green=slight risk of bias, dark green=low risk of bias. NA, not available.



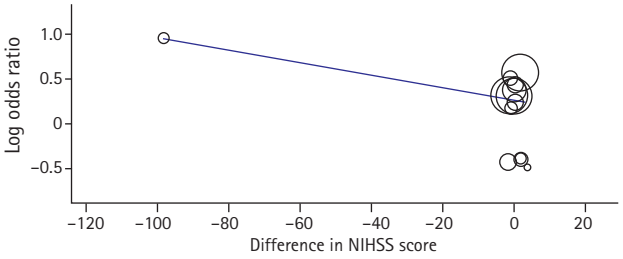
Supplementary Figure 2. Meta-regression analysis for differences of onset-to-needle time (ONT) means between study level groups. Coefficient: −0.013 (95% confidence interval, −0.025 to −0.00); SE, 0.006; *P*=0.048.



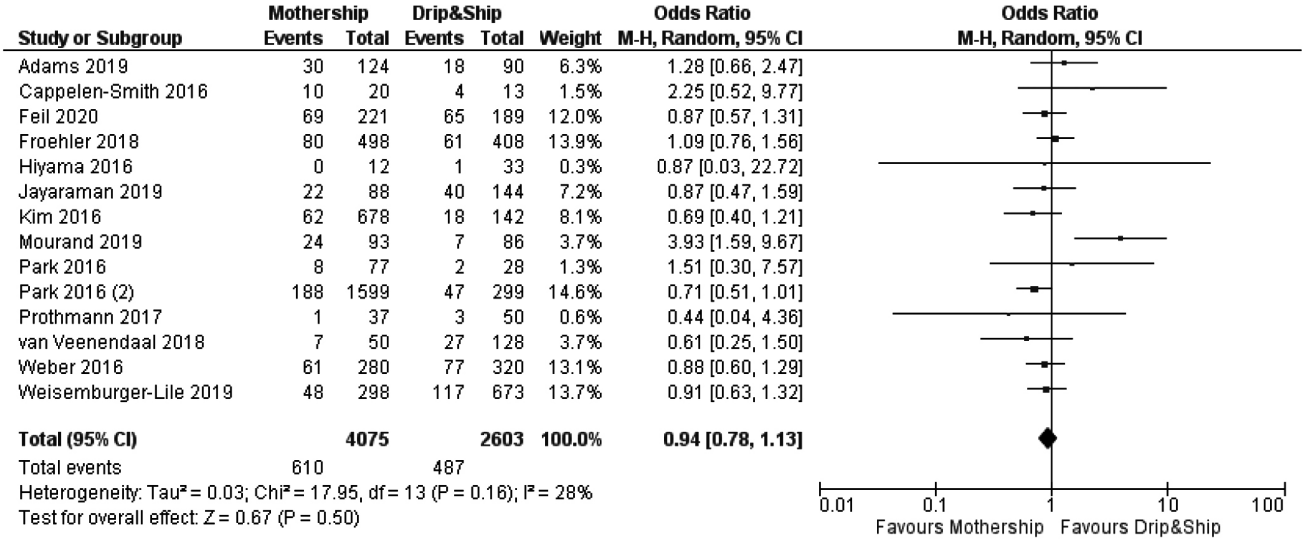
Supplementary Figure 3. Meta-regression analysis for differences of onset-to-groin time (OGT) means between study level groups. Coefficient: −0.001 (95% confidence interval, −0.007 to 0.005); SE, 0.003; *P*=0.9.



Supplementary Figure 4. Meta-regression analysis for differences of age. Coefficient: −0.051 (95% confidence interval, −0.125 to 0.002); SE, 0.004; *P*=0.179.



Supplementary Figure 5. Meta-regression analysis for differences of clinical severity. Coefficient: −0.007 (95% confidence interval, −0.001 to 0.003); SE, 0.005; *P*=0.176. NIHSS, National Institutes of Health Stroke Scale.



Study or Subgroup	Mothership Events	Total	Drip&Ship Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Adams 2019	30	124	18	90	6.3%	1.28 [0.66, 2.47]
Cappelen-Smith 2016	10	20	4	13	1.5%	2.25 [0.52, 9.77]
Feil 2020	69	221	65	189	12.0%	0.87 [0.57, 1.31]
Froehler 2018	80	498	61	408	13.9%	1.09 [0.76, 1.56]
Hiyama 2016	0	12	1	33	0.3%	0.87 [0.03, 22.72]
Jayaraman 2019	22	88	40	144	7.2%	0.87 [0.47, 1.59]
Kim 2016	62	678	18	142	8.1%	0.69 [0.40, 1.21]
Mourand 2019	24	93	7	86	3.7%	3.93 [1.59, 9.67]
Park 2016	8	77	2	28	1.3%	1.51 [0.30, 7.57]
Park 2016 (2)	188	1599	47	299	14.6%	0.71 [0.51, 1.01]
Prothmann 2017	1	37	3	50	0.6%	0.44 [0.04, 4.36]
van Veenendaal 2018	7	50	27	128	3.7%	0.61 [0.25, 1.50]
Weber 2016	61	280	77	320	13.1%	0.88 [0.60, 1.29]
Weisemburger-Lile 2019	48	298	117	673	13.7%	0.91 [0.63, 1.32]
Total (95% CI)		**4075**		**2603**	**100.0%**	**0.94 [0.78, 1.13]**
Total events	610		487			

Heterogeneity: Tau² = 0.03; Chi² = 17.95, df = 13 (P = 0.16); I² = 28%
Test for overall effect: Z = 0.67 (P = 0.50)

Supplementary Figure 6. Forest plot showing association of organizational paradigm with mortality at 3 months. M-H, Mantel-Haenszel; CI, confidence interval.

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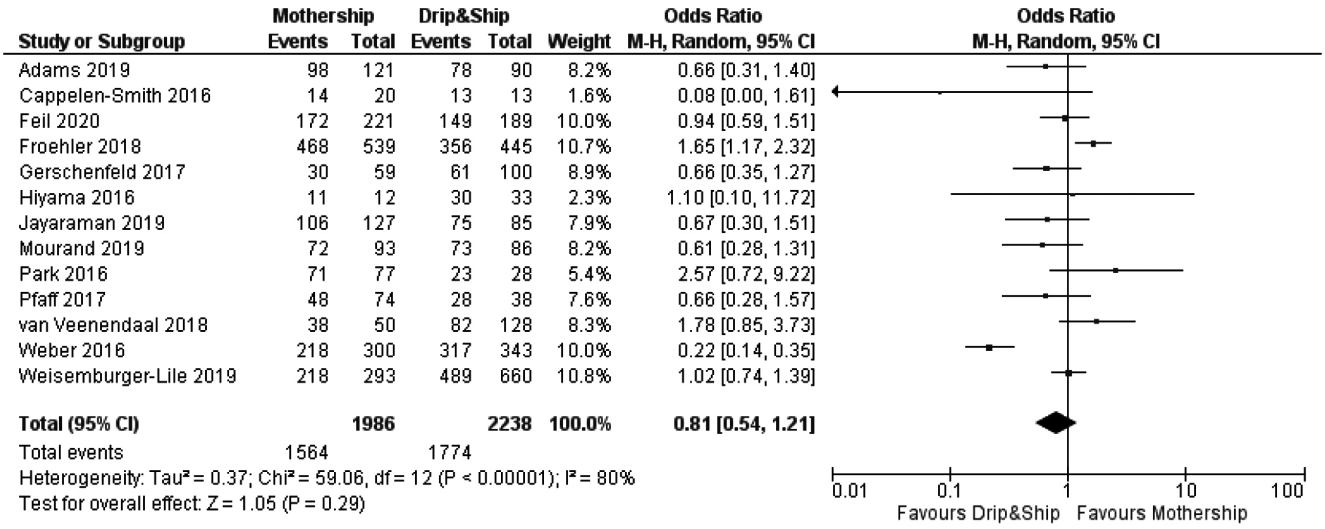
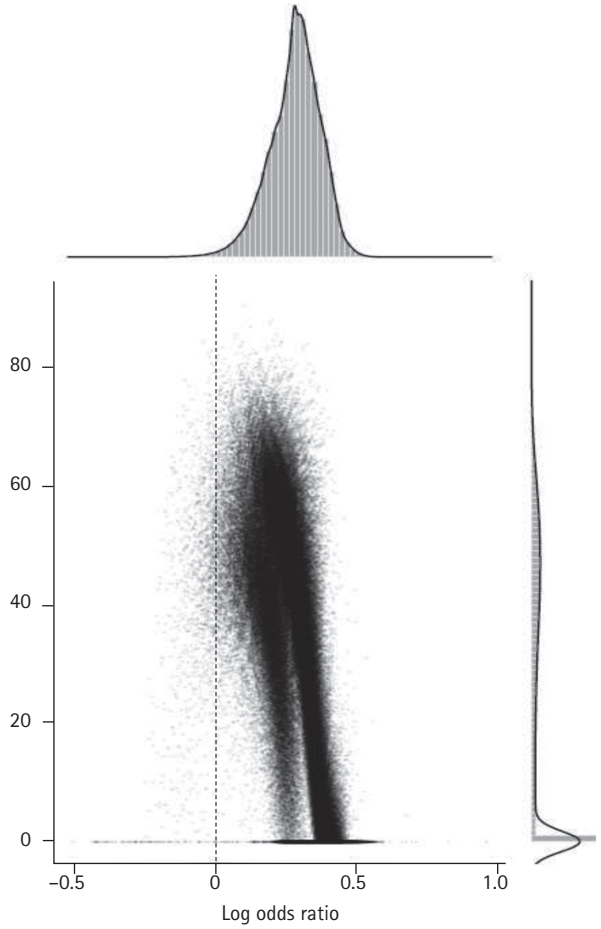
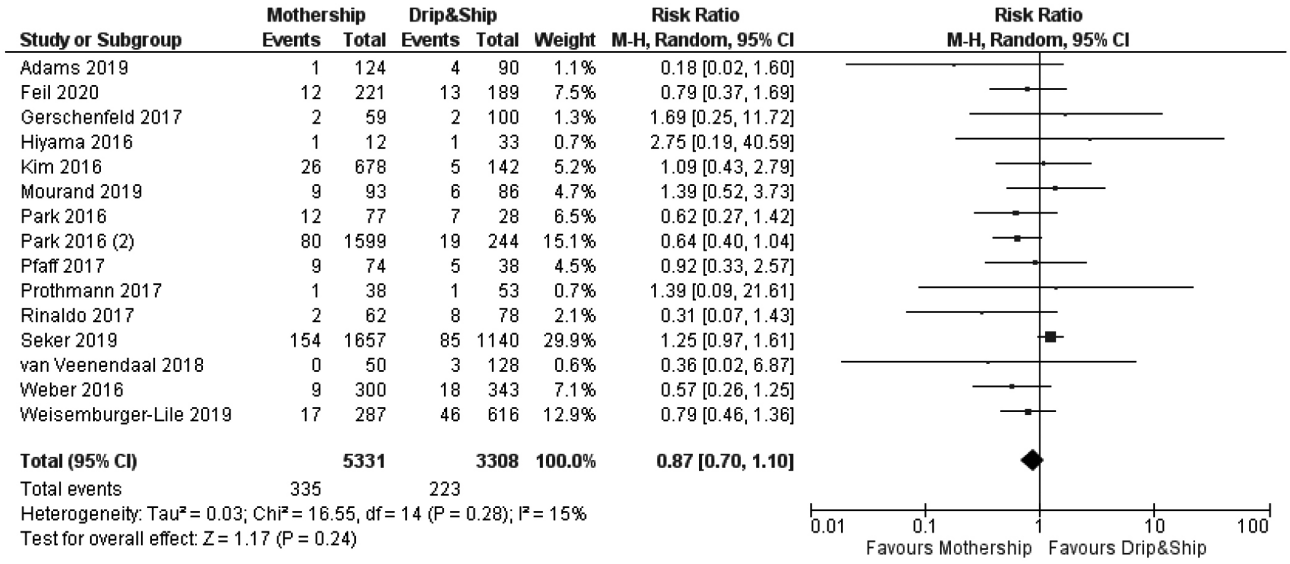


Supplementary Figure 7. Forest plot showing association of organizational paradigm with recanalization. M-H, Mantel-Haenszel; CI, confidence interval.



Supplementary Figure 8. Combinatorial analysis showing distribution of effect size and heterogeneity. The distribution of log odds ratio is in consistently in favor of mothership versus drip & ship paradigm for the primary outcome considered (good functional outcome, modified Rankin Scale 0–2).



Supplementary Figure 9. Forest plot for symptomatic intracerebral haemorrhage. M-H, Mantel-Haenszel; CI, confidence interval.

Supplementary Table 1. Leave-one out sensitivity analysis

Study	OR (95% CI)	tau^2	I^2
Adams et al. (2019)[10]	1.43 (1.28–1.59)	0.000	0.00
Cappelen-Smith et al. (2016)[19]	1.35 (1.18–1.55)	0.018	24.82
Feil et al. (2020)[11]	1.32 (1.14–1.54)	0.026	30.08
Froehler et al. (2017)[17]	1.33 (1.13–1.56)	0.032	32.67
Gerschenfeld et al. (2017)[21]	1.4 (1.24–1.58)	0.005	8.39
Hiyama et al. (2016)[22]	1.36 (1.19–1.55)	0.016	22.64
Jayaraman et al. (2020)[12]	1.33 (1.15–1.54)	0.024	29.52
Kim et al. (2016)[18]	1.32 (1.13–1.54)	0.028	31.67
Mourand et al. (2019)[14]	1.35 (1.17–1.55)	0.022	27.91
Park et al. (2016)[23]	1.35 (1.17–1.55)	0.020	25.87
Park et al. (2016)[24]	1.31 (1.16–1.48)	0.000	0.00
Pfaff et al. (2017)[16]	1.38 (1.22–1.57)	0.011	16.24
Prothmann et al. (2017)[26]	1.33 (1.16–1.53)	0.019	25.70
Rinaldo et al. (2017)[25]	1.35 (1.17–1.55)	0.020	26.31
Saver et al. (2015)[15]	1.33 (1.16–1.53)	0.021	26.75
van Veenendaal et al. (2018)[27]	1.33 (1.15–1.53)	0.022	28.14
Weber et al. (2016)[20]	1.33 (1.14–1.55)	0.028	31.72
Weisenburger-Lile et al. (2019)[13]	1.33 (1.13–1.56)	0.032	32.62

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