Direct mechanical thrombectomy in tPA ineligible and eligible patients versus the bridging approach: A Meta-analysis

Additional Information

Additional information 1 regarding search strategy and accessed databases

The following electronic databases were assessed: Ovid Medline, Pubmed, Web of Science Collection (Science Citation Index Expanded, Conference Proceedings Citation Index- Science, Book Citation Index– Science), ACP Journal Club, Database of Abstracts of Reviews of Effects, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Healtch Technology Assessment and NHS Economic Evaluation Database. A search strategy was formulated according to the PICO (population, intervention, comparison, outcome) framework[1]. The entered combination of MeSH terms and/or Keywords for each database in concordance with the PICO criteria is denoted in the supplementary Tables I-IV. Both, full research paper and conference abstracts were reviewed (without language restriction). Literature search was limited to the timeframe January 2007 to May 2017. The rationale underlying this restriction was the advent of second generation thrombectomy devices in 2007 (cf. study inclusion criteria).Systematic literature search was performed by a physician after specific training by the library services of the Clinical Trial Unit (Liberary&Information Services for the Institutes of Social & Preventive Medicine (ISPM), Primary Health Care (BIHAM) and CTU, Bern, Switzerland).

Additional information 2 regarding inclusion criteria

Prespecified inclusion criteria were: (1) the study reports comparative outcomes of dMTE vs. IVT+MTE, (2) the study is a randomized trial or a prospective or retrospective observational series; (3) the study reports at least on one primary outcome or two secondary outcomes along with patient age (see supplementary table V for primary and secondary outcomes), (4) the study reports on eligibility of dMTE patients for IVT, (5) a minimum of 10 patients per treatment arm, (6) most patients (≥80%) had been treated with 2nd generation thrombectomy devices (stent retrievers or aspiration).

Additional information 3 regarding study data and outcomes extracted

The following data, if available, were extracted: study year, type of study (retrospective observational, prospective observational, matched prospective observational, randomized controlled trial subgroup analysis), registry/study name, number of participating center(s), sample size and eligibility rates of dMTE patients for IV tPA. Furthermore, the following baseline characteristics and outcome parameters were extracted for the dMTE and the IVT+MTE group: age, risk factor history (including hypertension, diabetes, atrial fibrillation, and previous cerebrovascular event), preinterventional Alberta Stroke Program Early CT Score, site of occlusion, onset to puncture interval, door/imaging to puncture interval, admission NIHSS, rates of successful reperfusion (defined as Thrombolysis in Cerebral Infarction, TICI 2b/3), rate of complete reperfusion (TICI 3), rate of functional independence at day 90 (defined as mRSs≤2), mortality at day 90, symptomatic intracerebral hemorrhage (sICH) and asymptomatic intracerebral hemorrhage (aICH). We also extracted the grading systems applied by the investigators/authors for evaluation of reperfusion, radiological hemorrhage classification, and sICH classification.

We contacted 6 authors to request additional information. Two authors provided the full data set with numerical data, one author clarified rates of eligibility of IV tPA and three authors confirmed that all/most patients had been treated with 2nd generation devices.

Additional information 4 regarding influence analysis, heterogeneity assessment and evaluation of publication bias

Influence analysis was performed with each study deleted from the model once while exploring robustness of the summary estimates. Cochrane's Q, and I² (including 95% confidence intervals) statistics were calculated in order to evaluate study heterogeneity[2,3]. Both methods have been shown to have comparable control of Type I error rate and statistical power[4]. I² values of greater than 50% / 75% were rated as substantial / considerable heterogeneity, respectively. Forest plot and Doi plot visualization as well as Luis Furuya-Kanamori index (LFK index) calculation were performed to assess publication bias. According to the LFK index, plot asymmetry was rated as absent (LFK +/-1), minor asymmetry (LFK index exceeds ±1 but within ±2) or major asymmetry (LFK index exceeds +/-2)[5].

Additional information 5 regarding Quality assessment

For each study, the risk of bias was judged by XX according to the Cochrane collaboration tool for assessing risk of bias[6]. Although developed for randomized trials, the general structure of the tool is deemed also useful to follow when assessing non-randomized, observational studies, as per the Cochrane Handbook. The additional important source of potential bias of selection bias due to IVT ineligibility was rated separately. Additionally, the following study features potentially contributing to risk of bias were evaluated: (1) specification of eligibility criteria for MTE, (2) comparable baseline characteristics and risk factor distribution between both groups and (3) reporting as intention to treat.

Additional information 6 regarding results of the literature search

In the article rating process, there were 7 (5.3%) discrepancies between the initial raters, which were resolved by the third rater and by additionally contacting the respective corresponding authors.

No results from RCTs comparing dMTE with IVT+MTE in IVT-eligible patients were found. Two abstracts presented at the European Stoke Organization Conference 2017 yielded information about ongoing and planned RCTs (Multicenter Randomized Cinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands No IV [MR CLEAN-NO IV] and Solitaire™ With the Intention For Thrombectomy Plus Intravenous t-PA Versus DIRECT Solitaire™ Stent-retriever Thrombectomy in Acute Anterior Circulation Stroke [SWIFT-DIRECT], https://clinicaltrials.gov/ct2/show/NCT03192332)[7]. Also, one protocol was published of an RCT focused solely upon comparing dMTE with supportive medical therapy in IVT-ineligible patients[8]. However, the study was prematurely stopped after the enrollment of 4 patients[9].

Four RCTs met selection criteria by providing data permitting comparison of dMTE in enrolled IVT-IN patients with IVT+MTE in enrolled IVT-E patients[10–13]. For one of the older RCTs (SOLITAIRE™ FR With the Intention For Thrombectomy [SWIFT] Study), the data were reported pooled with observational data from another prospective registry[14], while for the other three data were solely from the most recent RCTs (Multicenter Randomized Cinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands [MR CLEAN][15], Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times [ESCAPE] and Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of

Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset [REVASCAT]). Six prospective observational studies met selection criteria (1 single center, 5 multi center). In addition, ten retrospective observational studies met selection criteria (7 single-center, 3 multi center). Two observational studies performed an analysis using a case-matching. One prospective observational study and two retrospective observational studies reported on IVT-E dMTE patients[16–18]. Reporting frequencies of outcome parameters and corresponding patient numbers are shown in supplementary Table V.

Additional information 7 regarding baseline characteristics and risk factor distribution

Among the 20 studies, only one reported an age difference, with dMTE patients significantly older than IVT+MTE patients[19]. (see Table 1 and standardized mean age difference denoted in supplementary Figure II). Similarly, admission NIHSS was comparable in dMTE and IVT+MTE patients in 18 of 20 studies. ASPECTS (reported in 4/20 studies) did only differ between dMTE and IVT+MTE patients in one study (see supplementary table VI). Overall, patients treated with dMTE had higher odds for a medical history of atrial fibrillation (sOR 1.94, 95%-CI 1.50-2.50, supplementary figure III) and prior cerebrovascular events (sOR 1.94, 95%-CI 1.60-2.35, supplementary figure IV), reported in 13 and 10 studies, respectively. Nominally higher rates of history of hypertension in dMTE patients did not reach statistical significance (sOR 1.09, 95%-CI 0.93-1.28, supplementary figure V). The odds for a history of diabetes were comparable between both groups (sOR 1.07, 95%-CI 0.75-1.54, supplementary figure VI). In 17 studies reporting on time metrics in IVT-IN dMTE vs IVT-E patients treated with IVT+MTE, onset to puncture intervals were comparable in 11, significantly longer in 4 studies in IVT-IN dMTE patients, and significantly longer in 2 studies in IVT-E patients treated with IVT+MTE (Table 1)[19–24]. All IVT-E studies reported shorter onset to puncture, door to puncture, and imaging to puncture metrics in the dMTE group than the IVT+MTE group (Table 1).

References

1. Schardt C, Adams MB, Owens T, Keitz S, Fontelo P. Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC Med Inform Decis Mak*. 2007;7(1):16. doi:10.1186/1472-6947-7-16.

2. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558. doi:10.1002/sim.1186.

3. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ Br Med J*. 2003;327(7414):557-560. doi:10.1136/bmj.327.7414.557.

4. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I^2 index? *Psychol Methods*. 2006;11(2):193-206. doi:10.1037/1082-989X.11.2.193.

5. Doi SAR, Barendregt JJ. Meta-analysis I. In: Doi SAR, Williams GM, eds. *Methods of Clinical Epidemiology*. Berlin, Heidelberg: Springer Berlin Heidelberg; 2013:229-252. doi:10.1007/978-3-642-37131-8_14.

6. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928. doi:10.1136/bmj.d5928.

7. Late Breaking Abstracts. *Eur Stroke J*. 2017;2(1_suppl):477-495. doi:10.1177/2396987317706897.

8. Bendszus M, Thomalla G, Knauth M, Hacke W, Bonekamp S, Fiehler J. Thrombectomy in patients ineligible for iv tPA (THRILL). *Int J Stroke*. 2015;10(6):950-955. doi:10.1111/ijs.12527.

9.   Bendszus M, Thomalla G, Hacke W, et al. Early termination of THRILL, a prospective study of mechanical thrombectomy in patients with acute ischemic stroke ineligible for i.v. thrombolysis. *Clin Neuroradiol*. 2016;26(4):499-500. doi:10.1007/s00062-016-0538-8.

10.   Coutinho JM, Liebeskind DS, Slater L-A, et al. Combined Intravenous Thrombolysis and Thrombectomy vs Thrombectomy Alone for Acute Ischemic Stroke: A Pooled Analysis of the SWIFT and STAR Studies. *JAMA Neurol*. 372(11):1009-1018. doi:10.1001/JAMANEUROL.2016.5374.

11.   Goyal M, Demchuk AM, Menon BK, et al. Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke for the ESCAPE Trial Investigators*. *N Engl J Med*. 2015;372:1019-1030. doi:10.1056/NEJMoa1414905.

12.   Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke. *N Engl J Med*. 2015;372(24):1-11. doi:10.1056/NEJMoa1503780.

13.   Mulder MJHL, Berkhemer OA, Fransen PSS, et al. Treatment in patients who are not eligible for intravenous alteplase: MR CLEAN subgroup analysis. *Int J Stroke*. 2016;11(6):637-645. doi:10.1177/1747493016641969.

14.   Coutinho JM, Liebeskind DS, Slater L-A, et al. Combined Intravenous Thrombolysis and Thrombectomy vs Thrombectomy Alone for Acute Ischemic Stroke A Pooled Analysis of the SWIFT and STAR Studies. *JAMA Neurol*. 2017;74(3):268-274. doi:10.1001/jamaneurol.2016.5374.

15.   Berkhemer OA, Fransen PSS, Beumer D, et al. A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke. *N Engl J Med*. 2014;372(1):141217070022009.

doi:10.1056/NEJMoa1411587.

16. Weber R, Nordmeyer H, Hadisurya J, et al. Comparison of outcome and interventional complication rate in patients with acute stroke treated with mechanical thrombectomy with and without bridging thrombolysis. *J Neurointerv Surg*. 2017;9(3):229 LP-233. http://jnis.bmj.com/content/9/3/229.abstract.

17. Broeg-Morvay A, Mordasini P, Bernasconi C, et al. Direct mechanical intervention versus combined intravenous and mechanical intervention in large artery anterior circulation stroke: A matched-pairs analysis. *Stroke*. 2016;47(4):1037-1044. doi:10.1161/STROKEAHA.115.011134.

18. Wang H, Zi W, Hao Y, et al. Direct endovascular treatment: an alternative for bridging therapy in anterior circulation large-vessel occlusion stroke. *Eur J Neurol*. 2017;24(7):935-943. doi:10.1111/ene.13311.

19. Alonso de Leciñana M, Martínez-Sánchez P, García-Pastor A, et al. Mechanical thrombectomy in patients with medical contraindications for intravenous thrombolysis: a prospective observational study. *J Neurointerv Surg*. November 2016:neurintsurg-2016-012727. doi:10.1136/neurintsurg-2016-012727.

20. Rai AT, Boo S, Buseman C, et al. Intravenous thrombolysis before endovascular therapy for large vessel strokes can lead to significantly higher hospital costs without improving outcomes. *J Neurointerv Surg*. 2017:neurintsurg-2016-012830. doi:10.1136/neurintsurg-2016-012830.

21. Saver JL, Goyal M, Bonafe A, et al. Stent-Retriever Thrombectomy after Intravenous t-PA vs. t-PA Alone in Stroke. *N Engl J Med*. 2015;372(24):2285-2295.

doi:10.1056/NEJMoa1415061.

22.   Abilleira S, Ribera A, Cardona P, et al. Outcomes After Direct Thrombectomy or Combined Intravenous and Endovascular Treatment Are Not Different. *Stroke*. 2017:STROKEAHA.116.015857. doi:10.1161/STROKEAHA.116.015857.

23.   Minnerup J, Wersching H, Teuber A, et al. Outcome After Thrombectomy and Intravenous Thrombolysis in Patients With Acute Ischemic Stroke: A Prospective Observational Study. *Stroke*. 2016;47(6):1584-1592. doi:10.1161/STROKEAHA.116.012619.

24.   Broeg-Morvay A, Mordasini P, Bernasconi C, et al. Direct mechanical intervention versus combined intravenous and mechanical intervention in large artery anterior circulation stroke: A matched-pairs analysis. *Stroke*. 2016;47(4):1037-1044. doi:10.1161/STROKEAHA.115.011134.

25.   Doi SAR, Barendregt JJ, Khan S, Thalib L, Williams GM. Advances in the meta-analysis of heterogeneous clinical trials I: The inverse variance heterogeneity model. *Contemp Clin Trials*. 2015;45:130-138. doi:10.1016/j.cct.2015.05.009.

26.   Pearl J. Causal inference in statistics: An overview. *Stat Surv*. 2009;3(0):96-146. doi:10.1214/09-SS057.

SUPPLEMENTAL TABLES

Supplementary Table I – PubMed Search Strategy

Population / Patient (problem, disease, coexisting problems)	"Stroke" [Mesh] **OR** Cerebrovascular event[Title/Abstract] OR Stroke[Title/Abstract] OR apoplex[Title/Abstract] OR CVA[Title/Abstract] OR cerebrovascular accident[Title/Abstract] OR brain vascular accident[Title/Abstract] OR brain isch*[Title/Abstract] OR brain infarc*[Title/Abstract] OR cerebral infarc*[Title/Abstract] OR cerebral isch* OR cerebral vessel occlusion[Title/Abstract] OR large vessel occlusion[Title/Abstract] OR intracranial isch*[Title/Abstract] OR intracranial infarction[Title/Abstract] OR intracranial vessel occlusion [Title/Abstract] OR brain vessel occlusion [Title/Abstract]
AND	
Intervention I (Therapy)	Thrombectomy [Mesh] **OR** Thrombectomy[Title/Abstract] OR thrombectomie* [Title/Abstract] OR mechanical[Title/Abstract] OR endovascular[Title/Abstract] OR embolectomy[Title/Abstract] OR intracranial intervention[Title/Abstract] OR Stent-retriever[Title/Abstract] OR stentretriever[Title/Abstract] OR preset[Title/Abstract] OR solitaire[Title/Abstract] OR trevo[Title/Abstract] OR catch[Title/Abstract]
AND	
Intervention II (Therapy)	Tissue Plasminogen Activator [Mesh] **OR** bridging*[Title/Abstract] OR thrombolysis[Title/Abstract] OR rtPA[Title/Abstract] OR tpA[Title/Abstract] OR rt PA[Title/Abstract] OR alteplase[Title/Abstract] OR bridging-therapy[Title/Abstract]OR plasminogen activator[Title/Abstract] or recombinant-plasminogen[Title/Abstract] OR plasminogen-activator [Title/Abstract]
AND	
Comparison	direct[Title/Abstract] OR combined[Title/Abstract] OR with[Title/Abstract] OR alone[Title/Abstract] OR combination[Title/Abstract] OR preceding[Title/Abstract] OR preinterventional[Title/Abstract] OR prior [Title/Abstract] OR before [Title/Abstract] OR previous [Title/Abstract] OR concomitant [Title/Abstract] or stand-alone [Title/Abstract] or together [Title/Abstract] or following [Title/abstract] or followed [Title/abstract]) or eligible [Title/abstract] or contraindication [Title/abstract] or ineligible [Title/abstract] or preproced*[Title/abstract] or preinterv*[Title/abstract] or prethrom*[Title/abstract] or pre-proced*[Title/abstract] or pre-inter*[Title/abstract] or pre-throm*[Title/abstract]
Filters: published in the last 10 years Articles found: 1011 17 may 2017	

Supplementary Table II – Ovid MEDLINE Search Strategy

Population / Patient (problem, disease, coexisting problems)	Exp Stroke OR (Cerebrovascular event OR Stroke OR apoplex OR CVA OR cerebrovascular accident OR brain vascular accident OR brain isch$ OR brain infarc$ OR cerebral infarc$ OR cerebral isch$ OR cerebral vessel occlusion OR large vessel occlusion OR intracranial isch$ OR intracranial infarction OR intracranial vessel occlusion OR brain vessel occlusion).tw
AND	
Intervention I (Therapy)	Exp thrombectomy OR (Thrombectomy OR thrombectomie$ OR mechanical OR endovascular OR embolectomy OR intracranial intervention OR Stent-retriever OR stentretriever OR preset OR solitaire OR trevo OR catch).tw
AND	
Intervention II (Therapy)	Exp tissue plasminogen activator OR (bridging$ OR thrombolysis OR rtPA OR tpA OR rt PA OR alteplase OR bridging-therapy OR plasminogen activator or recombinant-plasminogen OR plasminogen-activator).tw
AND	
Comparison	(direct OR combined OR with OR alone OR combination OR preceding OR preinterventional OR prior OR before OR previous OR concomitant or stand-alone or together or following or followed or eligible or contraindication or ineligible or preproced$ or preinterv$ or prethrom$ or pre-proced$ or pre-inter$ or pre-throm$).tw
Filters: published in the last 10 years Articles found: 1729	

Supplementary Table III – Web of Science Collection Search Strategy

Population / Patient (problem, disease, coexisting problems)	TS=(Cerebrovascular event OR Stroke OR apoplex OR CVA OR cerebrovascular accident OR brain vascular accident OR brain isch* OR brain infarc* OR cerebral infarc* OR cerebral isch* OR cerebral vessel occlusion OR large vessel occlusion OR intracranial isch* OR intracranial infarction OR intracranial vessel occlusion OR brain vessel occlusion)
AND	
Intervention I (Therapy)	TS=(Thrombectomy OR thrombectomie* OR mechanical OR endovascular OR embolectomy OR intracranial intervention OR Stent-retriever OR stentretriever OR preset OR solitaire OR trevo OR catch)
AND	
Intervention II (Therapy)	TS=(bridging* OR thrombolysis OR rtPA OR tpA OR rt PA OR alteplase OR bridging-therapy OR plasminogen activator or recombinant-plasminogen OR plasminogen-activator)
AND	
Comparison	TS=(direct OR combined OR with OR alone OR combination OR preceding OR preinterventional OR prior OR before OR previous OR concomitant or stand-alone or together or following or followed or eligible or contraindication or ineligible or preproced* or preinterv* or prethrom* or pre-proced* or pre-inter* or pre-throm*)
Filters: published in the last 10 years Articles found: 2188	

Supplementary Table IV – EBM Reviews Search Strategy

Databases included: Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment, NHS Economic Evaluation Database

Population / Patient (problem, disease, coexisting problems)	Exp Stroke OR (Cerebrovascular event OR Stroke OR apoplex OR CVA OR cerebrovascular accident OR brain vascular accident OR brain isch$ OR brain infarc$ OR cerebral infarc$ OR cerebral isch$ OR cerebral vessel occlusion OR large vessel occlusion OR intracranial isch$ OR intracranial infarction OR intracranial vessel occlusion OR brain vessel occlusion).tw
AND	
Intervention I (Therapy)	Exp thrombectomy OR (Thrombectomy OR thrombectomie$ OR mechanical OR endovascular OR embolectomy OR intracranial intervention OR Stent-retriever OR stentretriever OR preset OR solitaire OR trevo OR catch).tw
AND	
Intervention II (Therapy)	Exp tissue plasminogen activator OR (bridging$ OR thrombolysis OR rtPA OR tpA OR rt PA OR alteplase OR bridging-therapy OR plasminogen activator or recombinant-plasminogen OR plasminogen-activator).tw
AND	
Comparison	(direct OR combined OR alone OR combination OR preceding OR preinterventional OR prior OR before OR previous OR concomitant or stand-alone or together or following or followed or eligible or contraindication or ineligible or preproced$ or preinterv$ or prethrom$ or pre-proced$ or pre-inter$ or pre-throm$).tw
Filters: published in the last 10 years Articles found: 1729	

Supplementary Table V – Primary and Secondary Outcomes and respective reporting rates

Primary Outcomes	*Reporting frequency (studies)*	*Total n patients*	*Quantitative analysis performed*
- Successful reperfusion (TICI2b/3)	19/20	4220	√
- Day 90 mRS	17/20	4657	√
- Mortality at day 90	17/20	4929	√
- Symptomatic ICH	16/20	3903	√
Secondary Outcomes			
- Complete reperfusion (TICI 3)	9/20	1753	√
- Any type of ICH	15/20	3635	√
- Symptom-onset to groin puncture	17/20	4319	(√)
- Door/Imaging to groin-puncture	7/20	1232	(√)

Supplementary Table VI– ASPECTS distribution between dMTE and IVT+MTE patients

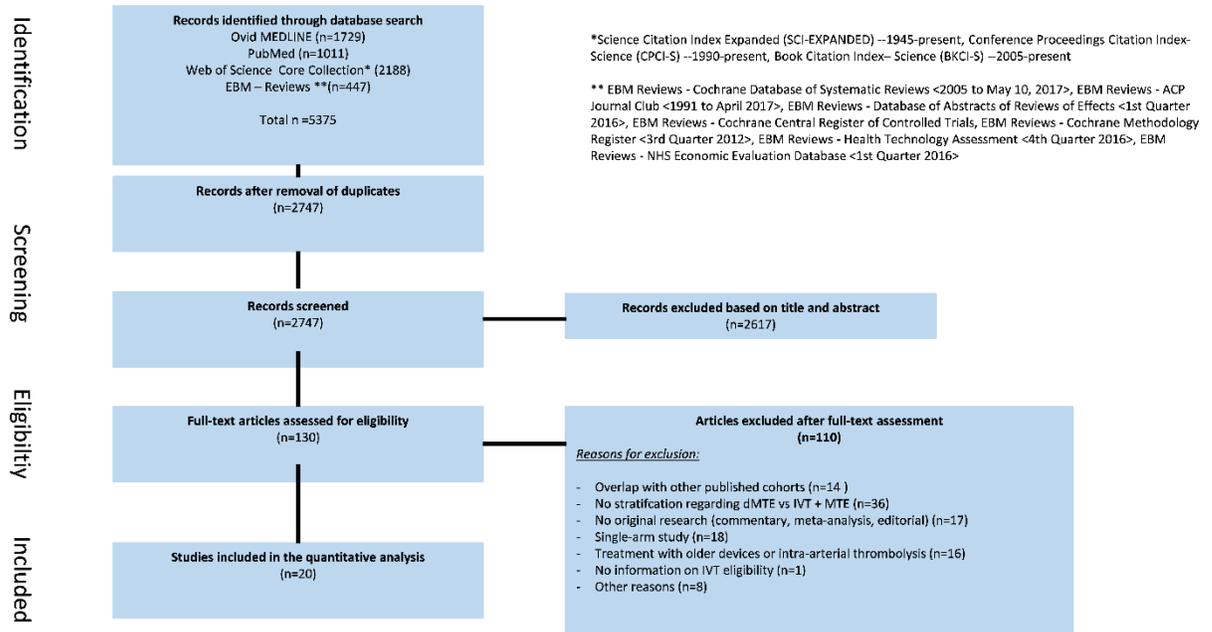| Study	ASPECTS		
	dMTE	IVT+MTE	p
Broeg-Morvay et al	N/A	N/A	N/A
Wang et al	9 (1-10)	9 (8-10)	0.61
Weber et al	N/A	N/A	N/A
Sanak et al	N/A	N/A	N/A
Coutinho et al	9 (8-10)	8 (7-10)	0.04
Abilleira et al	N/A	N/A	N/A
Kaesmacher et al	N/A	N/A	N/A
Behme et al	N/A	N/A	N/A
Guedin et al	N/A	N/A	N/A
Maier et al	8 (7-9)	8 (8-9)	N/A
Rai et al	7.5 (6-9)	8 (7-9)	0.09
Leker et al	N/A	N/A	N/A
Minnerup et al	N/A	N/A	N/A
Alonso de Lecinana et al	9 (8-10)	9 (8-10)	0.56
Davalos et al	7 (5-9)	7 (6-10)	N/A
Nogueira et al	N/A	N/A	N/A
Wee et al	N/A	N/A	N/A
Mulder et al	N/A	N/A	N/A
Goyal et al	N/A	N/A	N/A
Jovin et al	N/A	N/A	N/A

Supplementary Table VII – Risk of bias evaluation

|		Broeg-Morvay et al	Wang et al	Weber et al	Sanak et al	Coutinho et al	Abilleira et al	Kaesmacher et al	Behme et al	Guedin et al	Maier et al	Rai et al	Leker et al	Minnerup et al	Alonso deLecinana et al	Davalos et al	Nogueira et al	Wee et al	Mulder et al	Jovin et al	Goyal et al
Cochrane risk of bias (adapted)	Random sequence generation	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Treatment allocation according to ineligibility for IV rtPA (selection bias)	+	+	+/-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Blinding of participants and personnel (performance bias)	-	-	-	?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Blinding of outcome assessment (detection bias)	-	-	+	?	+	-	-	-	-	-	-	-	+	-	+/-	-	-	+	+	+
	Incomplete outcome data (attrition bias)	+	+	?	?	+	+	-	-	+	+	+	+	+	+	+	+	-	+	+	+
	Selective reporting (Reporting bias)	-	-	-	?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Other bias	Eligibility criteria specified	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
	Baseline characteristics similar between groups	+	+	+/-	?	-	-	+	+	+	-	-	-	-	-	?	-	+	-	-	-
	Reported as intention to treat	+	-	-	?	+	-	+	-	-	-	+	-	+	+	+	-	+	+	+	+

+, low risk of bias, - high risk of bias, +/- depending on groups or outcome: Weber et al., + for IVT eligible patients, - for IVT ineligible patients, Davalos et al. some primary and secondary outcomes were core lab assessed, some were not.
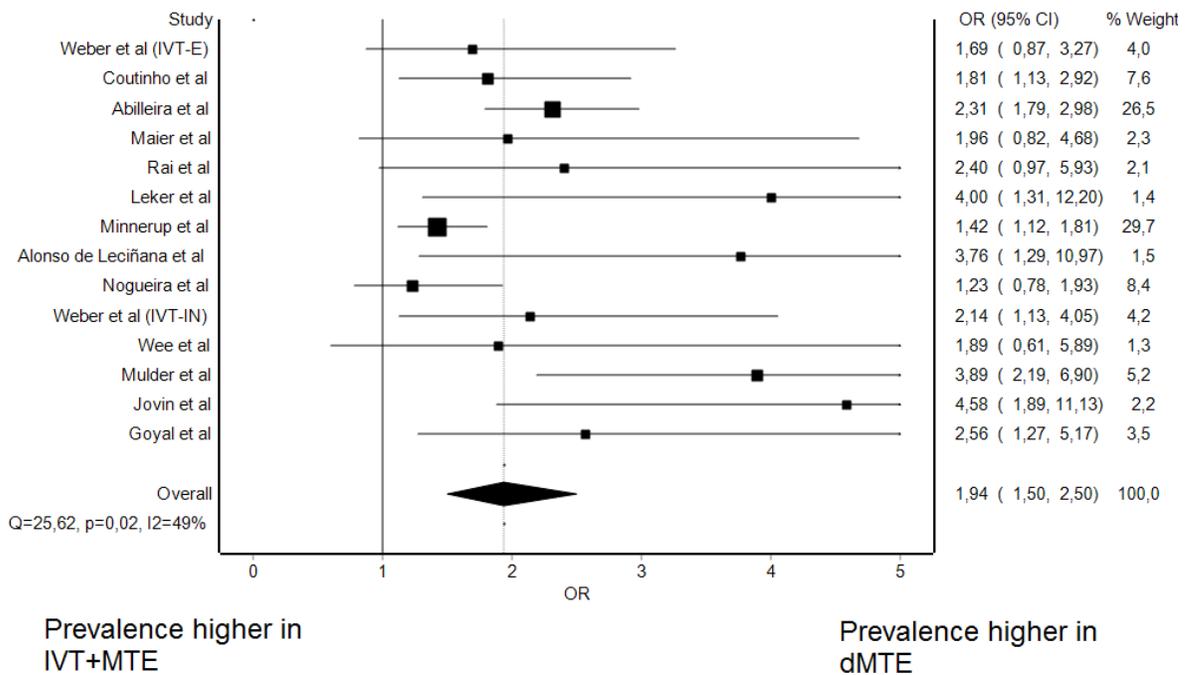
SUPPLEMENTAL FIGURES

Supplementary Figure I – Study flow chart according to PRISMA guidelines: Eligibility of studies was evaluated by two independent readers. Seven discrepancies were solved by a third rater and by contacting the corresponding authors.

Identification

Records identified through database search
Ovid MEDLINE (n=1729)
PubMed (n=1011)
Web of Science Core Collection* (2188)
EBM – Reviews **(n=447)

Total n =5375

*Science Citation Index Expanded (SCI-EXPANDED) --1945-present, Conference Proceedings Citation Index-Science (CPCI-S) --1990-present, Book Citation Index– Science (BKCI-S) --2005-present

** EBM Reviews - Cochrane Database of Systematic Reviews <2005 to May 10, 2017>, EBM Reviews - ACP Journal Club <1991 to April 2017>, EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>, EBM Reviews - Cochrane Central Register of Controlled Trials, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>

Records after removal of duplicates
(n=2747)

Screening

Records screened
(n=2747)

Records excluded based on title and abstract
(n=2617)

Eligibility

Full-text articles assessed for eligibility
(n=130)

Articles excluded after full-text assessment
(n=110)
Reasons for exclusion:

- Overlap with other published cohorts (n=14)
- No stratifcation regarding dMTE vs IVT + MTE (n=36)
- No original research (commentary, meta-analysis, editorial) (n=17)
- Single-arm study (n=18)
- Treatment with older devices or intra-arterial thrombolysis (n=16)
- No information on IVT eligibility (n=1)
- Other reasons (n=8)

Included

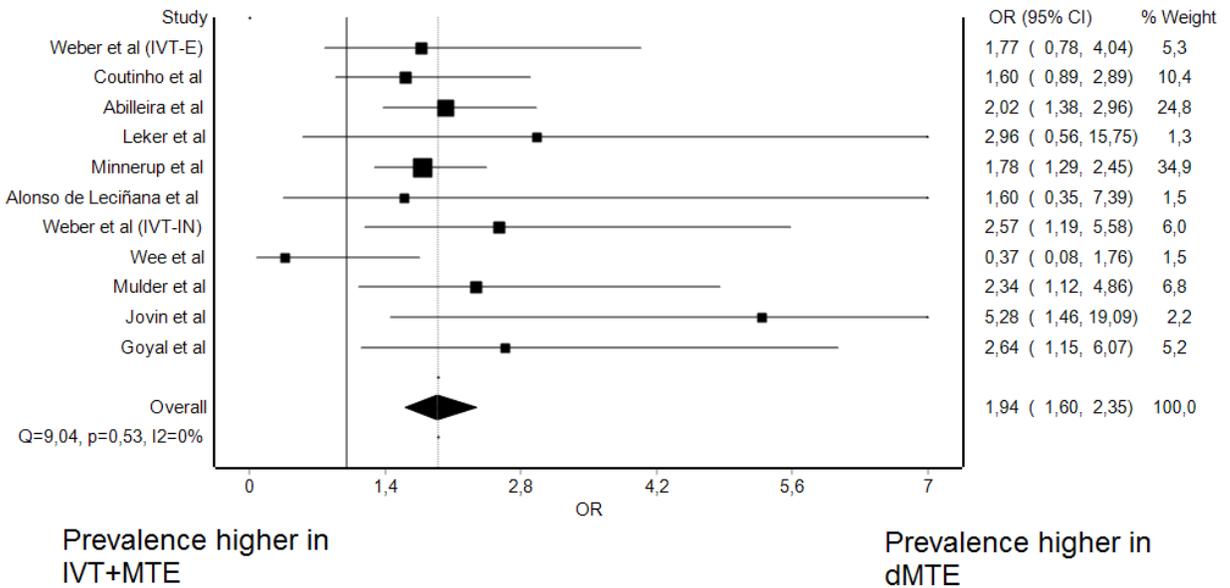**Studies included in the quantitative analysis**
(n=20)

Supplementary Figure II – Standardized mean difference of patient age between dMTE and MTE + IVT patients (calculated using Hedges' adjusted g)
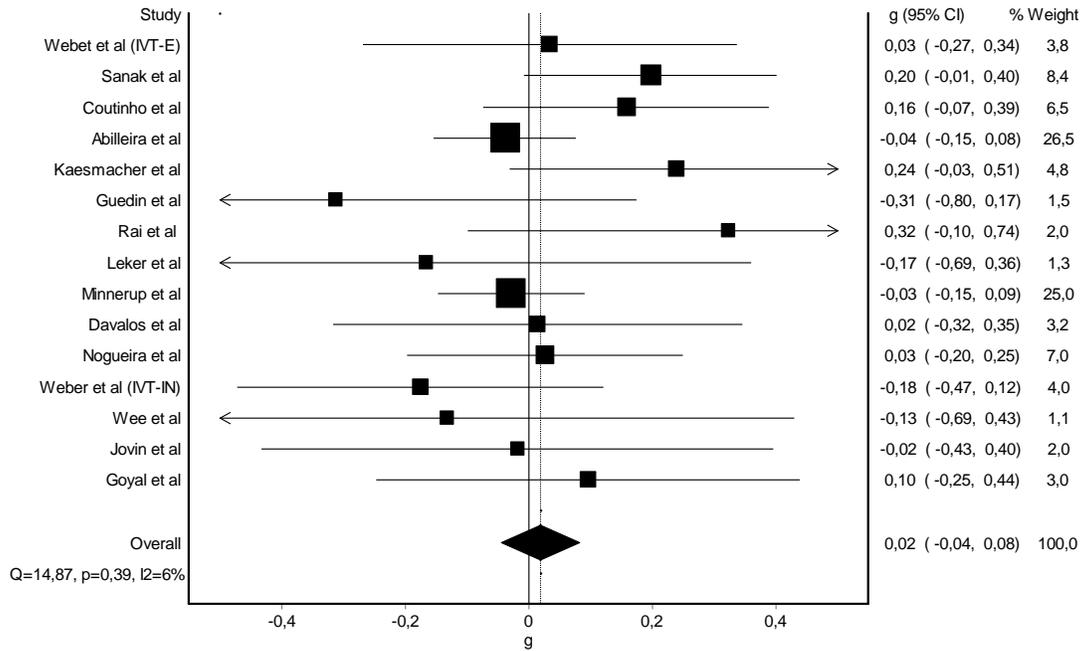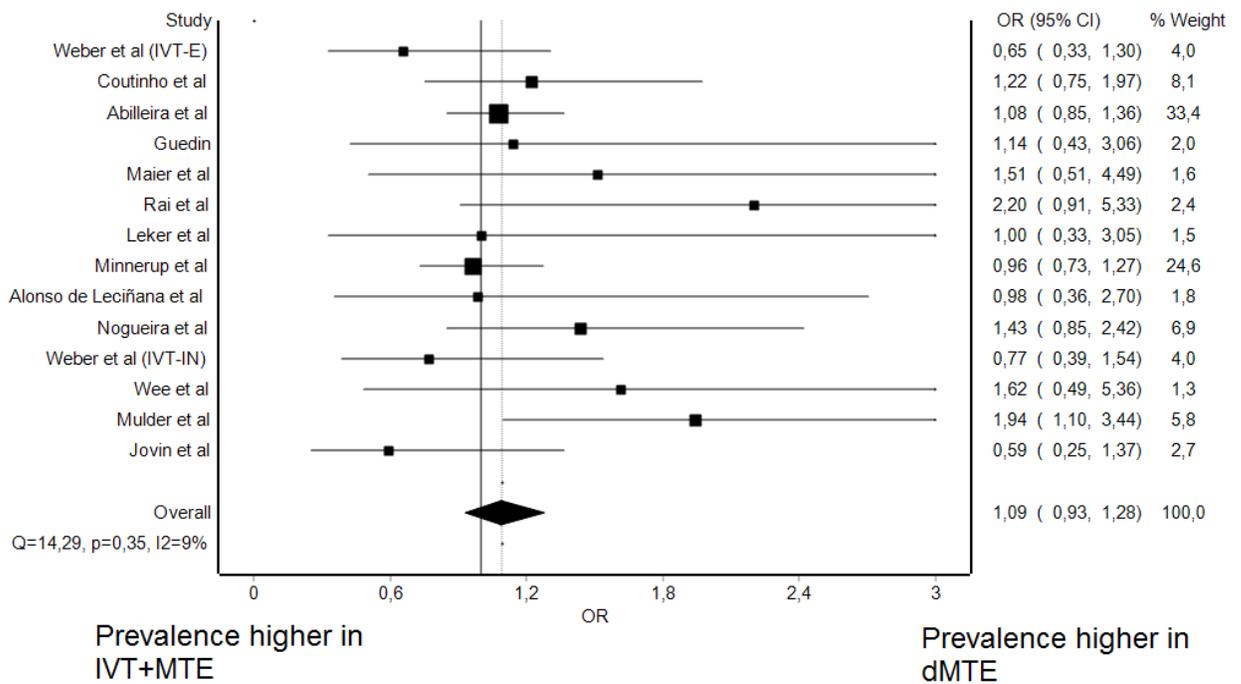

Supplementary Figure III – summary Odds Ratio for a medical history of atrial fibrillation in dMTE patients
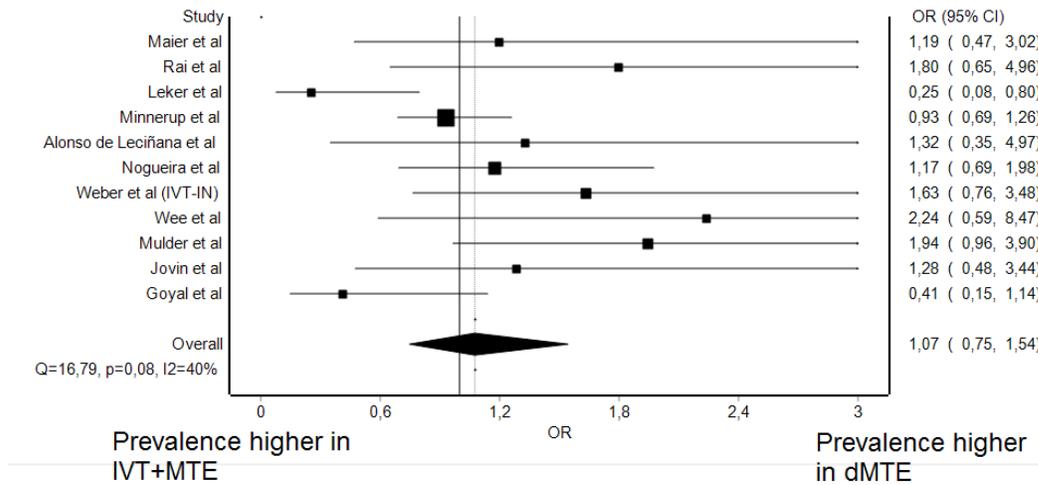
Supplementary Figure IV - summary Odds Ratio for a medical history of previous stroke or transient ischemic attack in dMTE patients


Study	OR (95% CI)	% Weight
Weber et al (IVT-E)	1,77 (0,78, 4,04)	5,3
Coutinho et al	1,60 (0,89, 2,89)	10,4
Abilleira et al	2,02 (1,38, 2,96)	24,8
Leker et al	2,96 (0,56, 15,75)	1,3
Minnerup et al	1,78 (1,29, 2,45)	34,9
Alonso de Leciñana et al	1,60 (0,35, 7,39)	1,5
Weber et al (IVT-IN)	2,57 (1,19, 5,58)	6,0
Wee et al	0,37 (0,08, 1,76)	1,5
Mulder et al	2,34 (1,12, 4,86)	6,8
Jovin et al	5,28 (1,46, 19,09)	2,2
Goyal et al	2,64 (1,15, 6,07)	5,2
Overall	1,94 (1,60, 2,35)	100,0

Q=9,04, p=0,53, I2=0%

Supplementary Figure V - summary Odds Ratio for a medical history of arterial hypertension in dMTE patients

| Study	OR (95% CI)	% Weight
Weber et al (IVT-E)	0,65 (0,33, 1,30)	4,0
Coutinho et al	1,22 (0,75, 1,97)	8,1
Abilleira et al	1,08 (0,85, 1,36)	33,4
Guedin	1,14 (0,43, 3,06)	2,0
Maier et al	1,51 (0,51, 4,49)	1,6
Rai et al	2,20 (0,91, 5,33)	2,4
Leker et al	1,00 (0,33, 3,05)	1,5
Minnerup et al	0,96 (0,73, 1,27)	24,6
Alonso de Leciñana et al	0,98 (0,36, 2,70)	1,8
Nogueira et al	1,43 (0,85, 2,42)	6,9
Weber et al (IVT-IN)	0,77 (0,39, 1,54)	4,0
Wee et al	1,62 (0,49, 5,36)	1,3
Mulder et al	1,94 (1,10, 3,44)	5,8
Jovin et al	0,59 (0,25, 1,37)	2,7
Overall	1,09 (0,93, 1,28)	100,0

Q=14,29, p=0,35, I2=9%

24

Supplementary Figure VI - summary Odds Ratio for a medical history of diabetes in dMTE patients

Supplementary Figure VII – summary Odds Ratio for d90 mRS≤2 in dMTE patients (post-hoc RCT analyses only)
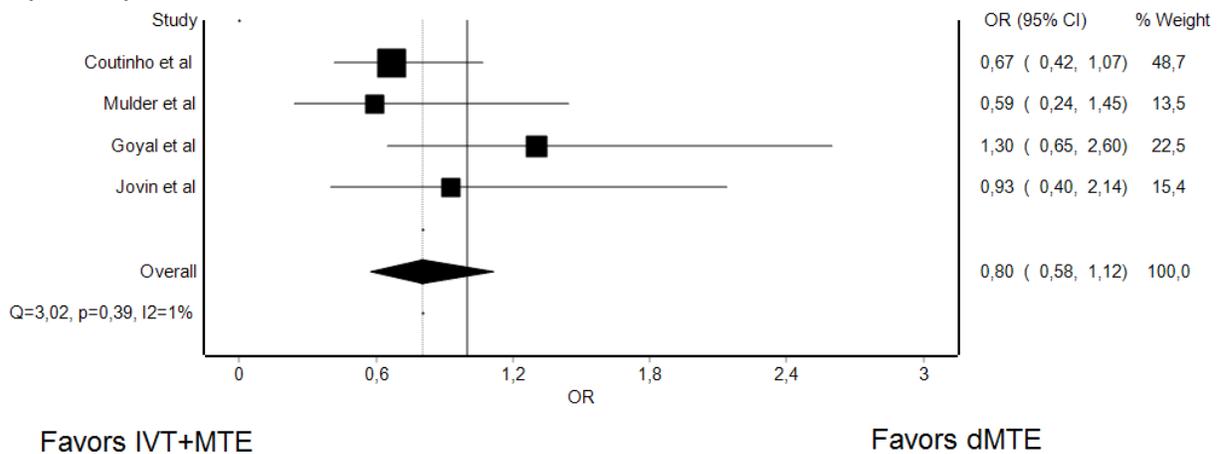

Supplementary Figure VIII – summary Odds Ratio for d90 mortality in dMTE patients (post-hoc RCT analyses only)
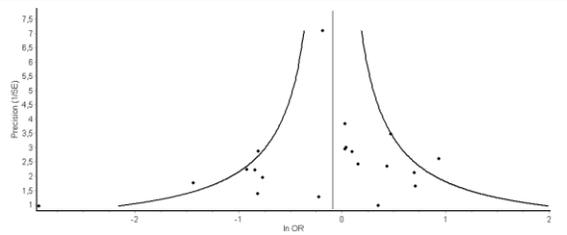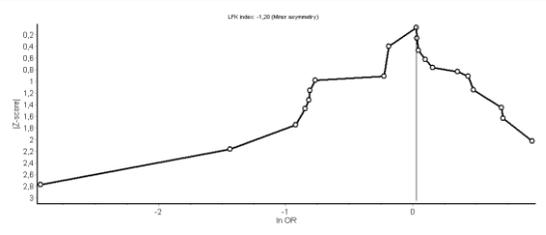
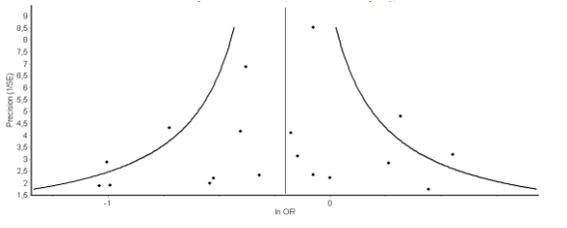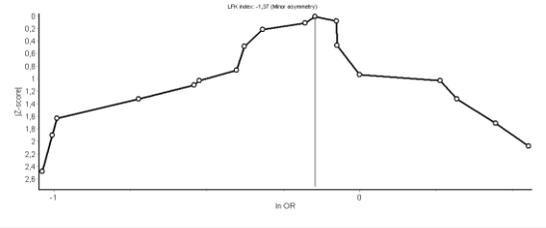**Supplementary Figure IX** – summary Odds Ratio for successful reperfusion of dMTE patients (post-hoc RCT analyses only)

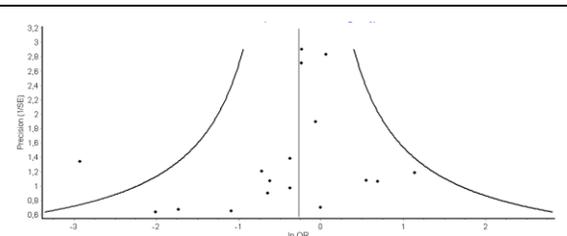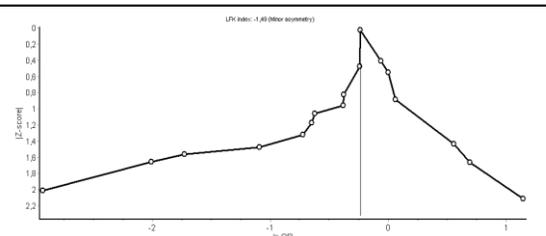**Supplementary Figure X** – summary Odds Ratio for TICI 3 reperfusion in dMTE patients
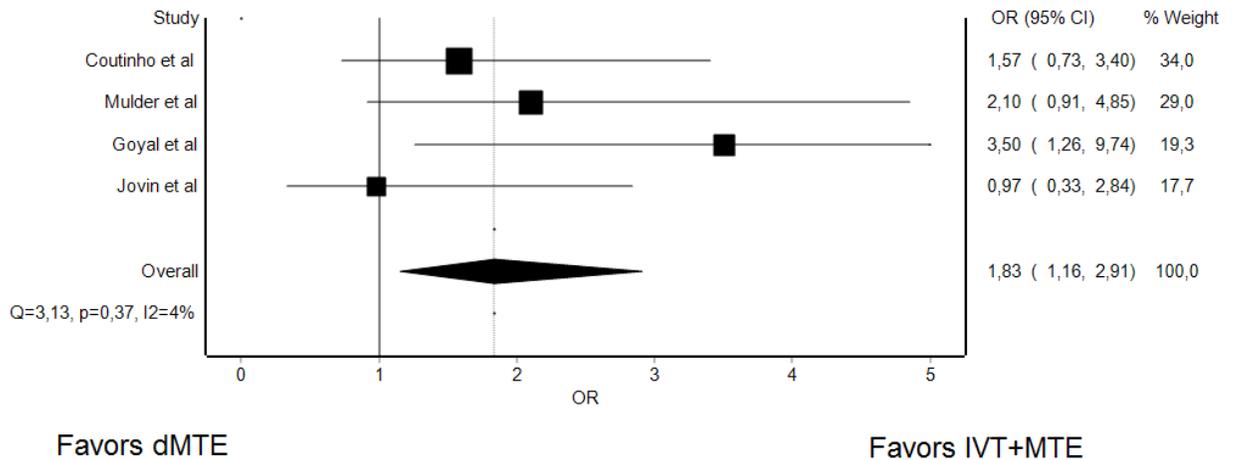
Supplementary Figure XI – summary Odds Ratio of dMTE patients for asymptomatic intracerebral hemorrhage

*matched-pair analysis; IVT-E, IVT eligible dMTE patients; IVT-IN, IVT ineligible dMTE patients
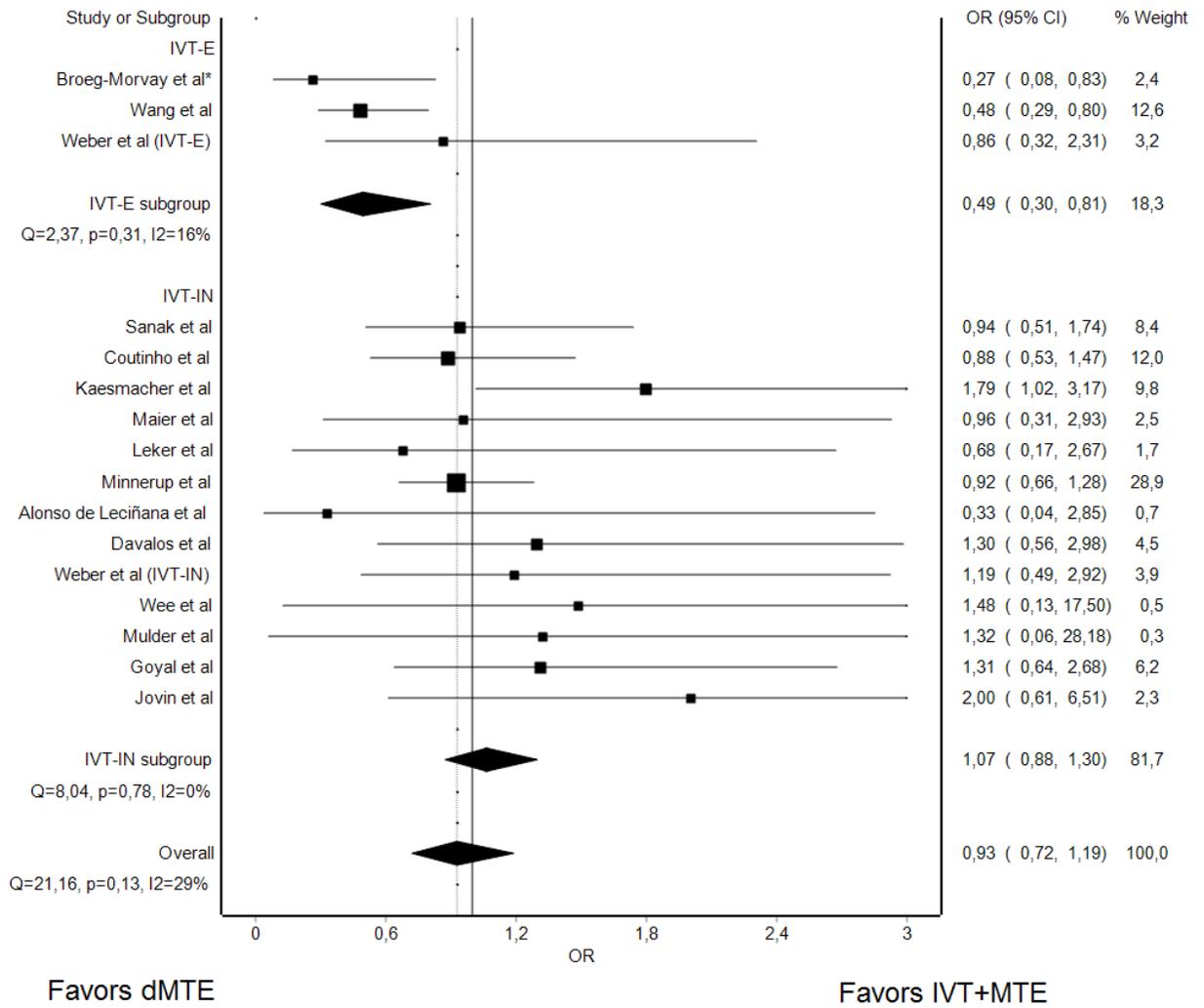
Supplementary Figure XII – funnel and doi plot analyses for the assessment of publication bias

	funnel plot	DOI plot	LFK
SR			-1,20 (minor asymmetry)
mRS90			-1,37 (minor asymmetry)
Mortality			0,52 (no asymmetry)
sICH			-1,49 (minor asymmetry)
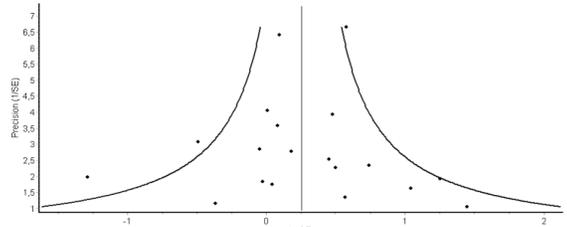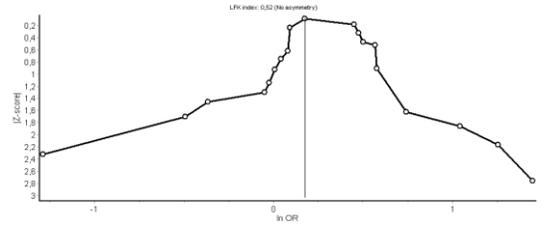
SR, successful reperfusion; mRS90, modified Rankin Scale at day 90 ≤2, sICH, symptomatic intracranial hemorrhage