Safety and efficacy of IA fibrinolytics as adjunct to mechanical thrombectomy: A systematic review and meta-analysis of observational data

Supplementary Information I – Search Strategy

Search Strategy:

PubMed

P Population / Patient (problem, disease, coexisting problems)	("endovascular procedures"[MeSH Major Topic] OR thrombectomy[Title/Abstract] OR Mechanical thrombectomy[Title/Abstract] OR endovascular[Title/Abstract] OR endovascular procedures[Title/Abstract] OR endovascular procedure[Title/Abstract] OR endovascular treatment[Title/Abstract] OR aspiration[Title/Abstract] OR large vessel occlusion[Title/Abstract] OR Recanalization[Title/Abstract] OR recanalization[Title/Abstract] OR revascularization[Title/Abstract] OR Reperfusion[Title/Abstract] OR intra-arterial[Title/Abstract] OR intra-arterial treatment[Title/Abstract] OR intervention[Title/Abstract] OR stentriever[Title/Abstract] OR interventional neuroradiology[Title/Abstract] OR thrombolytic therapy[Title/Abstract] OR stent-retriever[Title/Abstract] OR stentretriever OR solitaire[Title/Abstract] OR Trevo[Title/Abstract] OR preset[Title/Abstract] OR embotrap OR aspiration or ACE or sofia[Title/Abstract]) AND
I Intervention I (Therapy)	(intra-arterial thrombolysis[Title/Abstract] OR intra-arterial thrombolytics[Title/Abstract] OR intra-arterial tPA[Title/Abstract] OR intra-arterial uPA[Title/Abstract] OR intra-arterial tissue plasminogen activator [Title/Abstract] OR intra-arterial prourokinase[Title/Abstract] OR intra-arterial r-proUK[Title/Abstract]OR intraarterial thrombolysis[Title/Abstract] OR intraarterial thrombolytics[Title/Abstract] OR intraarterial tPA[Title/Abstract] OR intraarterial uPA[Title/Abstract] OR intraarterial tissue plasminogen activator [Title/Abstract] OR intraarterial prourokinase[Title/Abstract] OR intraarterial r-proUK[Title/Abstract] OR intra-arterial rt-PA[Title/Abstract] OR Intra-Arterial Alteplase[Title/Abstract] OR Rescue Therapy[Title/Abstract]) AND
C **Comparison**	/
O **Outcome**	("Intracranial Hemorrhages"[Mesh] OR intracerebral haemorrhage[Title/Abstract] OR intracerebral hemorrhage[Title/Abstract] OR Symptomatic intracerebral haemorrhage[Title/Abstract] OR Symptomatic intracerebral hemorrhage[Title/Abstract] OR intracranial haemorrhage[Title/Abstract] OR intracranial hemorrhage[Title/Abstract] OR hemorrhagic OR haemorrhagic OR mortality[Title/Abstract])

Filters: (("2000/01/01"[PDAT] : "2020/01/01"[PDAT])
AND
(German[lang] OR English[lang] OR French[lang] OR Spanish[lang]))

Results: 430

Embase

P Population / Patient (problem, disease, coexisting problems)	('thrombectomy':ab,ti OR 'Mechanical thrombectomy':ab,ti OR 'endovascular':ab,ti OR 'endovascular procedures':ab,ti OR 'endovascular procedure':ab,ti OR 'endovascular treatment':ab,ti OR 'aspiration':ab,ti OR 'large vessel occlusion':ab,ti OR 'Recanalization':ab,ti OR 'recanalization':ab,ti OR 'revascularization':ab,ti OR 'Reperfusion':ab,ti OR 'intra-arterial':ab,ti OR 'intra-arterial treatment':ab,ti OR 'intervention':ab,ti OR 'stentriever':ab,ti OR 'interventional neuroradiology':ab,ti OR 'thrombolytic therapy':ab,ti) AND
I Intervention I (Therapy)	('intra-arterial thrombolysis':ab,ti OR 'intra-arterial thrombolytics':ab,ti OR 'intra-arterial tPA':ab,ti OR 'intra-arterial uPA':ab,ti OR 'intra-arterial tissue plasminogen activator':ab,ti OR 'intra-arterial prourokinase':ab,ti OR 'intra-arterial r-proUK':ab,ti OR 'intraarterial thrombolysis':ab,ti OR 'intraarterial thrombolytics':ab,ti OR 'intraarterial tPA':ab,ti OR 'intraarterial uPA':ab,ti OR 'intraarterial tissue plasminogen activator':ab,ti OR 'intraarterial prourokinase':ab,ti OR 'intraarterial r-proUK':ab,ti OR 'intra-arterial rt-PA':ab,ti OR 'Intra-Arterial Alteplase':ab,ti OR 'Rescue Therapy':ab,ti) AND
C **Comparison**	/
O **Outcome**	('intracerebral haemorrhage':ab,ti OR 'intracerebral hemorrhage':ab,ti OR 'Symptomatic intracerebral haemorrhage':ab,ti OR 'Symptomatic intracerebral hemorrhage':ab,ti OR 'intracranial haemorrhage':ab,ti OR 'intracranial hemorrhage':ab,ti OR 'hemorrhagic' OR 'haemorrhagic' OR 'mortality':ab,ti)

Filters:

- study type: human
- publication type: article

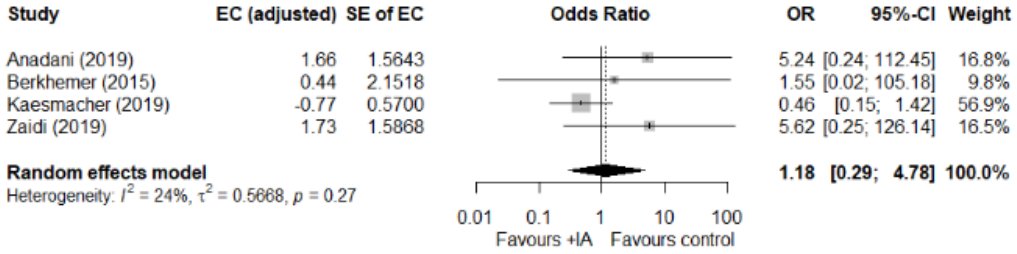
date range: 01.01.2000 onwards; date last searched: 01.01.2020

Results: 95 (270 duplicates with PubMed)

Supplementary Information II – Adjusted estimates for safety outcomes

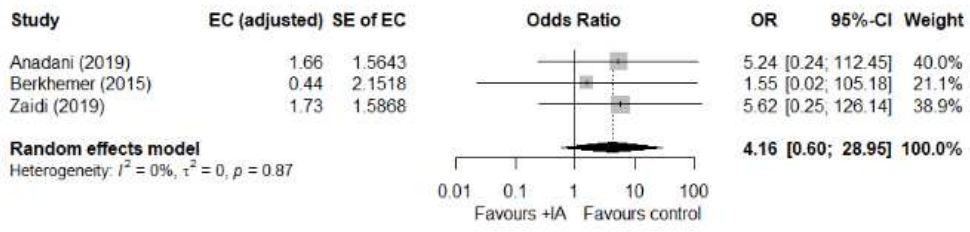
Using adjusted estimates, provided by four studies, the point estimate changed to aOR 1.47, 95%-CI 0.23-9.43, with three tPA studies suggesting numerically increased rates of sICH, although not statistically significant and with large uncertainty (aOR 5.24, 95%-CI 0.24-112.45 and aOR 5.62, 95%-CI 0.25-126.12, and aOR 1.55, 95%-CI 0.02-105.2, respectively). The adjusted summary estimate of these tPA studies regarding occurrence of sICH was 4.16, 95%-CI 0.60-28.95. Using adjusted estimates for mortality (provided by four studies), there was no difference in the rates of day 90 mortality (aOR 0.66, 95%-CI 0.40-1.08).

Supplementary Information II Figure 1– Summary estimate for sICH considering adjusted estimates



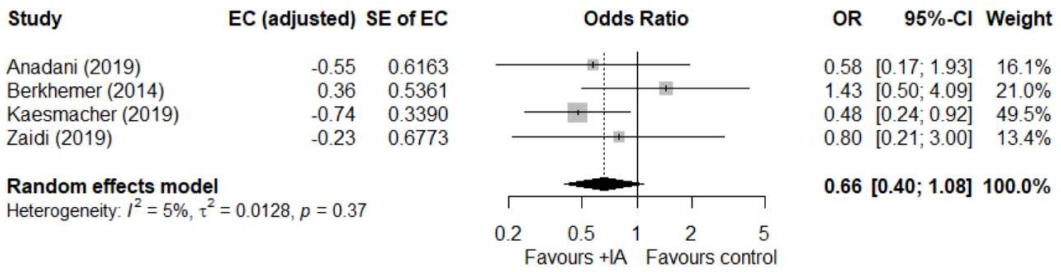
EC, estimated coefficient; SE, standard error; IA, intra-arterial fibrinolytics

Supplementary Information II Figure 2– Summary estimate for sICH considering adjusted estimates (only tPA)



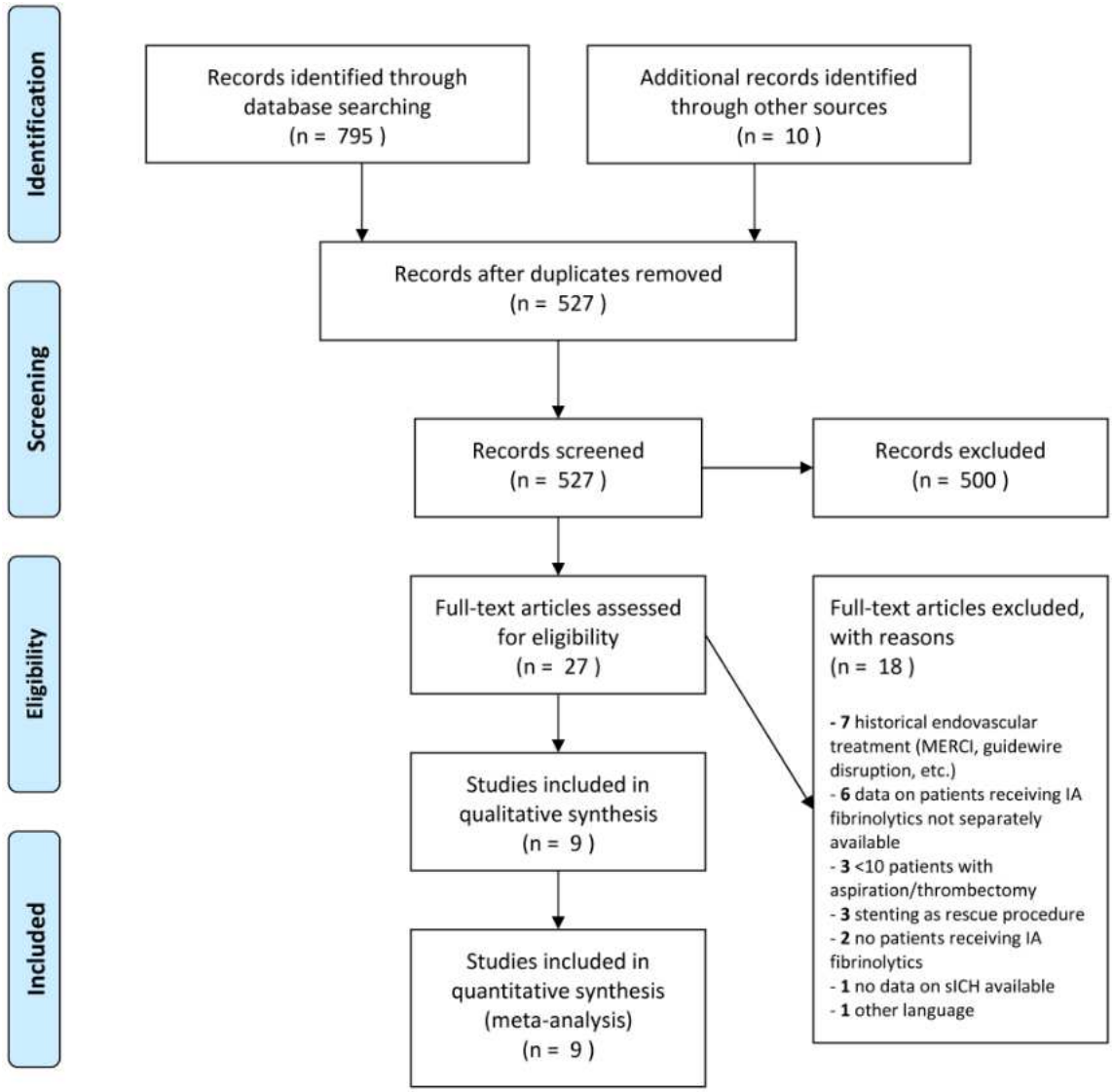
EC, estimated coefficient; SE, standard error; IA, intra-arterial fibrinolytics

Supplementary Information II Figure 3– Summary estimate for Mortality considering adjusted estimates



EC, estimated coefficient; SE, standard error; IA, intra-arterial fibrinolytics

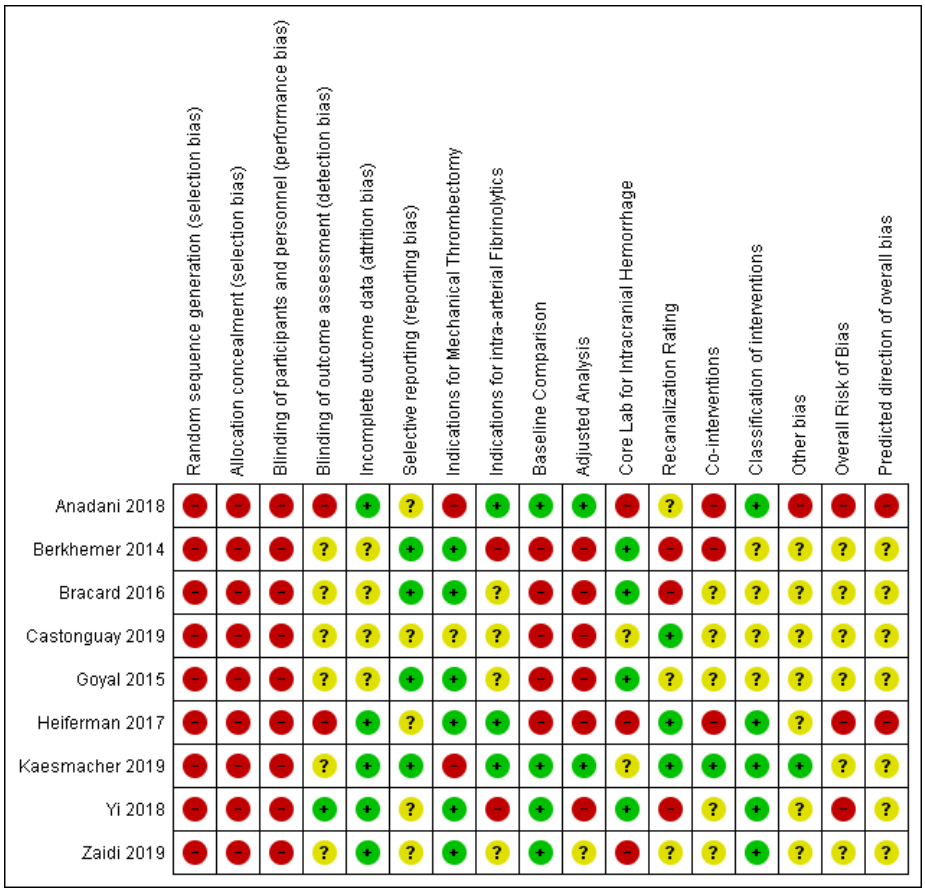
Supplementary Figure I – PRISMA Flow Chart



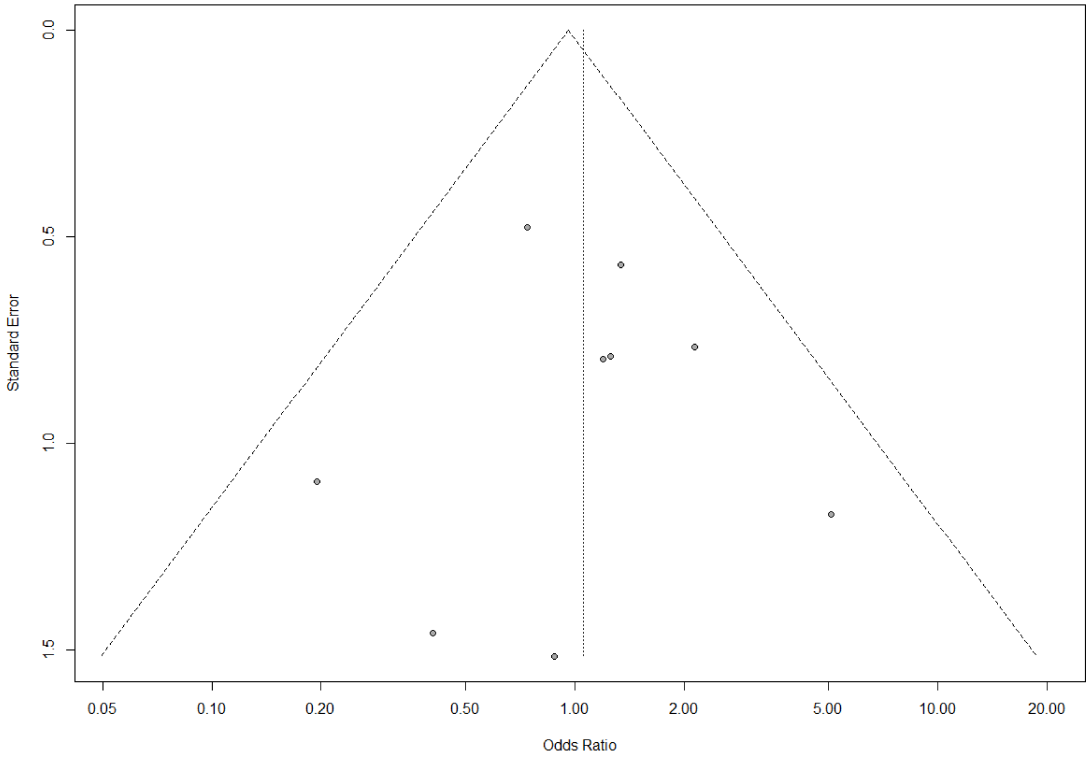
Other sources:

- HERMES collaboration original articles and supplementary material to evaluated if the study protocol allowed for the use of intra-arterial fibrinolytics.
- Manual hand search of abstracts of the European Stroke Conference, World Stroke Conference, American Stroke Association and American Heart Association International Stroke Conference, SNIS Annual Meeting and WFITN annual meeting during the last 3 years.

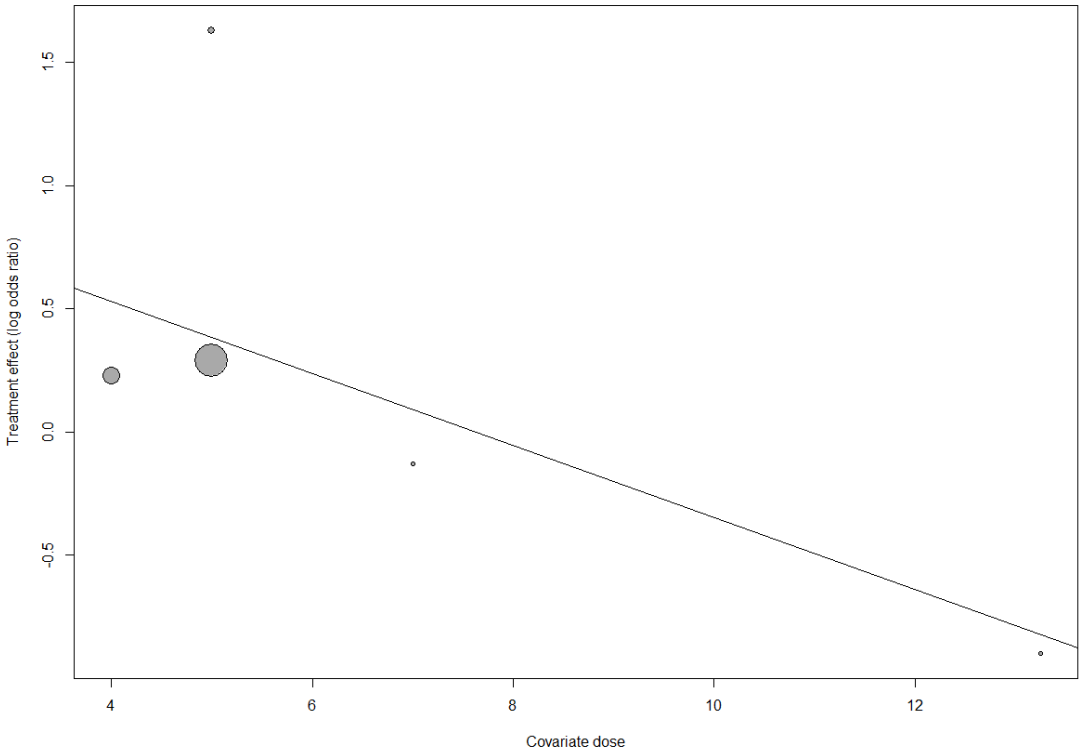
Supplementary Figure II - Robins-I risk of bias (adapted for observational studies)



Supplementary Figure III – Funnel Plot for the primary outcome sICH

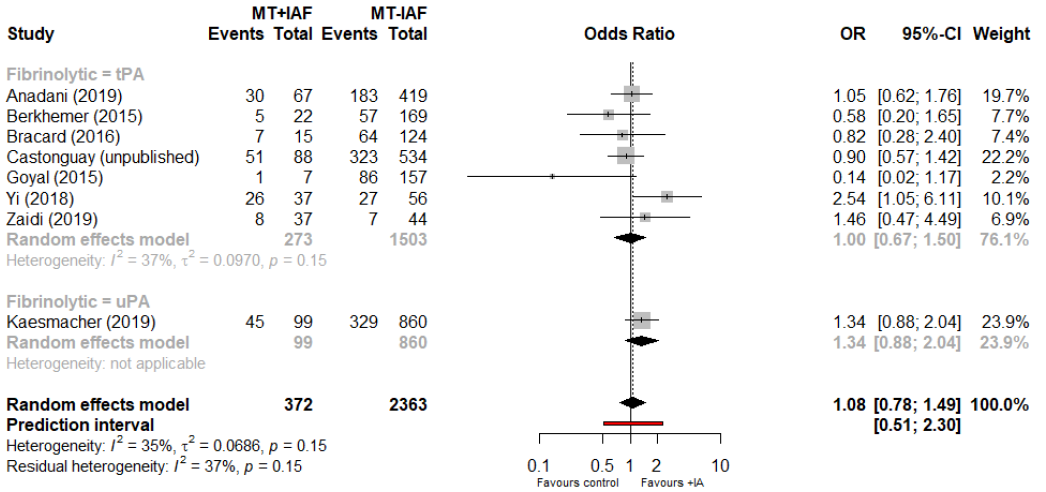


Supplementary Figure IV – Bubble blot on median dose and treatment effect of added intra-arterial fibrinolytics on sICH



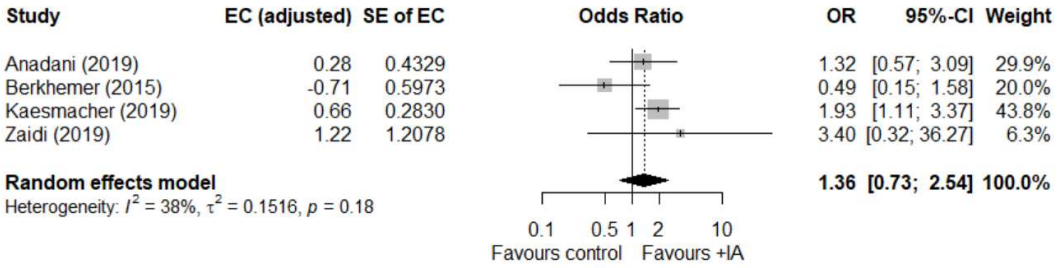
Treatment effect of MT+IAF vs MT-IAF (y-axis) with different median doses of tPA (in mg, x-axis) applied. There was no statistical significance evidence of an increased rate of sICH in the MT+IAF arm in higher doses. However, subgroups are small and dose range was confined to 4-13.25mg median doses only.

Supplementary Figure V – Forest plot of unadjusted odds ratios for functional independence (mRS 0-2) at three months in patients with and without adjunctive administration of intra-arterial fibrinolytics during MT



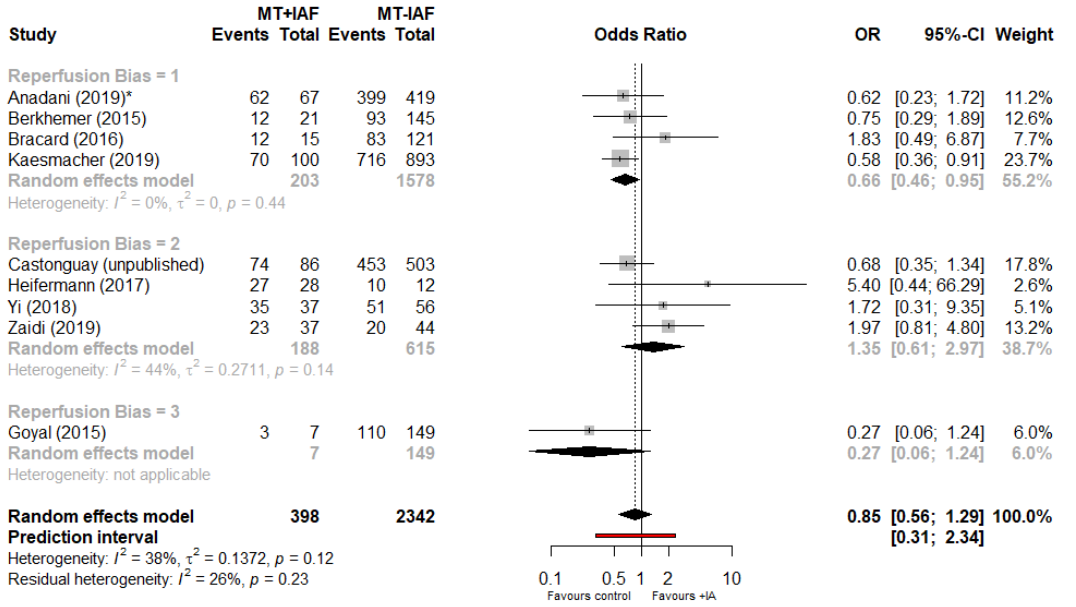
MT: Mechanical Thrombectomy, IAF: IA Fibrinolytics, tPA: tissue plasminogen-activator, uPA: Urokinase, OR: odds ratio

Supplementary Figure VI – Summary estimate for functional independence considering adjusted estimates



EC, estimated coefficient; SE, standard error; IA, intra-arterial fibrinolytics

Supplementary Figure VII –Forest plot of unadjusted odds ratios for successful reperfusion (TICI2b/3) in patients with and without adjunctive administration of intra-arterial fibrinolytics during MT



MT: Mechanical Thrombectomy, IAF: IA Fibrinolytics, tPA: tissue plasminogen-activator, Reperfusion bias 1 refers to studies reporting on patients with the primary intention to improve unsuccessful or incomplete reperfusion (high risk of reperfusion bias towards poor TICI grades in the IA groups), Reperfusino bias 2 refers to studies including patients where IA fibrinolytics were mainly applied during or before initial stent-retriever deployment or studies in which the control group of patients without IA fibrinolytics also consisted of patients with unsuccessful or incomplete MT patients (low risk of reperfusion bias towards poor TICI grades in the IA group), Reperfusion bias 3 refers to studies with an unknown risk of reperfusion bias.

Supplementary Table I – Additional study characteristics

Study	MT Technique	Reason for administering IA fibrinolytics	Baseline difference	Mode of adjustment	Imaging selection / Core Size	Definition of sICH
Anadani et al.[17]	ADAPT	Incomplete reperfusion after MT at operator discretion taking into account baseline characteristics	- Poor TICI grades in the + IA group - Better ASPECTS in + IA group - Less IV tPA pretreatment in + IA group	Matched-pair analysis with matching on ASPECT, IV tPA use, site of occlusion and final mTICI	Overall ASPECTS ≥6 in >88%, with ≥90% in the IA arm	ECASS (HI1, HI2, PH1, PH2), no sICH available
Heiferman et al.[31]	Stent-retriever thrombectomy	Operators discretion at three time points during the procedure: (1) upon catheterization of the cervical internal carotid artery, (2) at stentriever clot engagement, and (3) postrecanalization	none	Not performed	N/A	sICh was assigned when patients had a decline in neurologic examination related to the postprocedural intracranial hemorrhage
Yi et al.[21]	Stent-retriever thrombectomy	Operators discretion during the initial temporary stent deployment	- More Hyperlipidemia in + IA group - More IV tPA pretreatment in + IA group	Multivariable linear regression analysis for procedure time	N/A	Symptomatic intracerebral hemorrhage was defined as a type 2 parenchymal hematoma within 36 h after treatment combined with an increased NIHSS score of at least 4 points from baseline or as any subarachnoid hemorrhage associated with clinical symptoms
Zaidi et al.[16]	Stent-retriever thrombectomy	As rescue after failed MT	- Onset to Puncture shorter in + IA group - Systolic and diastolic blood pressure lower in + IA group	Cohort matching on M1 occlusions only and groin puncture of 8 hours or less	N/A	sICH was defined as any parenchymal hematoma, subarachnoid hemorrhage, or intraventricular hemorrhage associated with a worsening of the National Institutes of Health Stroke Scale (NIHSS) by ≥4-points within 24-hours
Kaesmacher et al.[33]	>90% Stent-retriever thrombectomy	- Rescue after thrombectomy (TICI0/1): 15.0% (15/100) - Improvement TICI2a/2b: 53.0% (53/100) - Before/during first/second/third stent-retriever deployment: 25.0% (25/100) - Treatment of ENTs: 7.0% (7/100)	- Younger patients, more females, lower platelets, shorter symptom-onset to admission, longer groin to reperfusion and poorer TICI grades in + IA group	Multivariable logistic regression	Median ASPECTS 8 (IQR 5-9) , with median ASPCETS 7 in the IA Urokinase group	sICH was defined as evidence of intracranial hemorrhage with a 4-point or more increase on the total National Institutes of Health Stroke Scale (NIHSS) score or a 1-point increase in level of consciousness on the NIHSS
Bracard et al. [27]	77.1% stent-retriever thrombectomy 9.3% aspiration 13.6% multiple systems	A complementary IA injection of a maximum of 0·3 mg/kg of tPA at the end of thrombectomy was authorized only in cases of persistent distal occlusions.	Not reported	Not available	>50% of patients with ASPECTS 8-10	Symptomatic hemorrhage was defined as visible intracranial bleeding on CT or MRI plus an increase in the NIHSS score of at least 4 points.
Berkhemer et al.[26]	Stent-retriever thrombectomy	Rescue treatment in case of incomplete reperfusion or distal embolisms after MT	Younger age in +IA group	Multivariable logistic regression, adjusted for age, sex, baseline NIHSS	Median ASPECTS 9 (IQR 7-10)	Any evidence of intracranial hemorrhage with NIHSS deterioration of ≥4

Goyal et al.[25]	Stent-retriever thrombectomy	Not available	Not available	Not available	Median ASPECTS 9 (IQR 8-10)	ICH by site-determination which meant any clinical deterioration (not specified by NIHSS score) which was attributed to the ICH
Castonguay et al.[30]	Stent-retriever thrombectomy	- Rescue after Medtronic stent-retriever 18.9% (18/95) - Rescue after another rescue device, 1.1% (1/95) - Primary in conjunction with initial deployment of the Medtronic stent-retriever, 74.7% (71/95) - Other, 1.1% (1/95)	Not available	Not available	>90% of patients with ASPECTS ≥6	Any PH1, PH2, RIH, SAH, or IVH associated with a 4 points or more

Table 2 – Summary of angiographic efficacy

Study including reports of more detailed angiographic efficacy analysis	Qualitative summary
Yi et al.	- higher rates of successful reperfusion achieved with two or less device passes (81.1% vs 51.8%, P=.004) - shorter puncture to recanalization times in the group additionally treated with IA tPA (median 49 vs 89 min, P=.003)[22]
Heiferman et al.	- tendency for higher TICI3 scores for the primary combined approach (MT+ IA tPA) as opposed to controls (20/28, 71% vs 5/12, 42%, P for overall TICI grade difference .059)[32].
Zaidi et al.	- Additional IA tPA applied in 37/81 patients was associated with higher rates of successful reperfusion (61.2% vs 46.6%). - There was a significant difference, when analysis was confined to M1 occlusions only (77.8% vs 38.9%, P=0.02)[16]. Additionally, recanalization times where shorter in the IA tPA group.
Kaesmacher et al.	- In 68 cases in whom IA Urokinase was administered after failed or incomplete MT, IA Urokinase improved reperfusion in 40/68 (58.8%) patients[34]. - Reperfusion improvement led to a TICI change in 26/68 (38.2%) patients. - In addition, in seven patients treated with IA Urokinase for emboli to new territory (ENT), four patients showed reperfusion[34].