Stroke , Thrombolysis and devices

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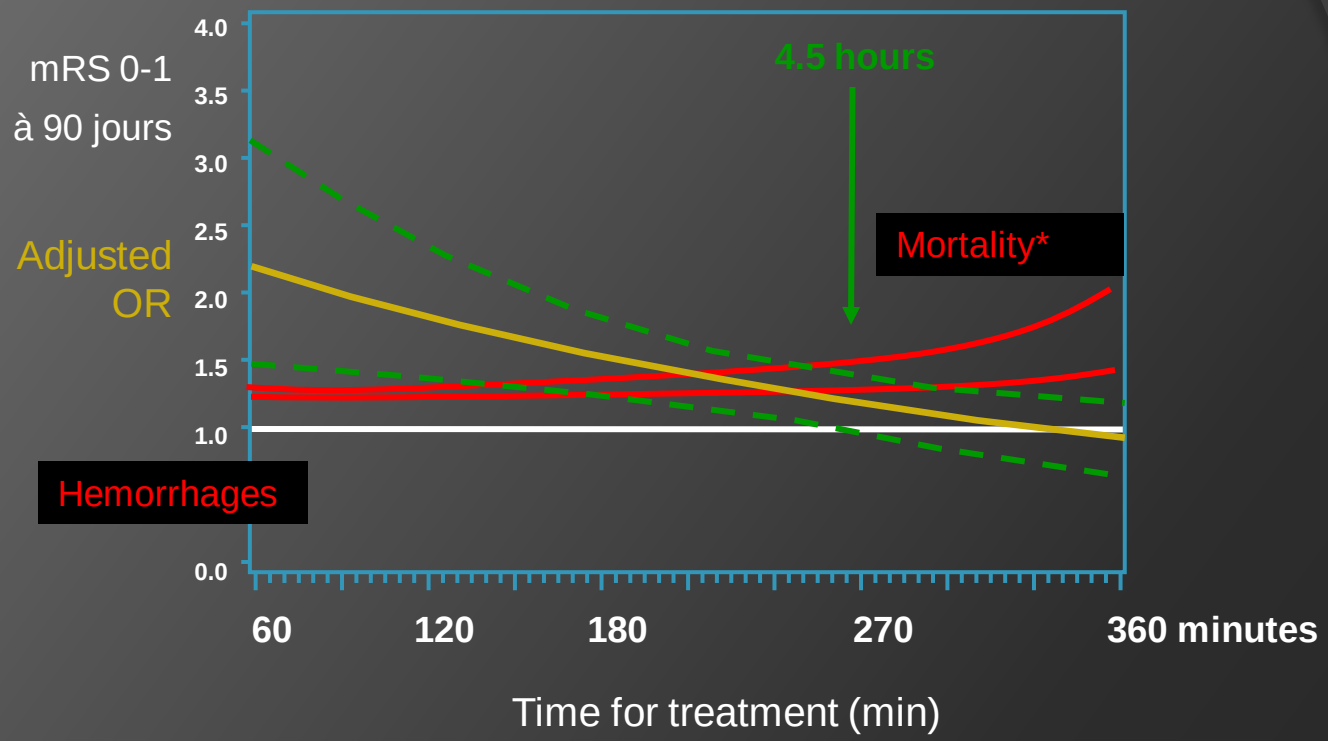
Conflict of interest: none

IV Thrombolysis and endovascular thrombectomy

- approved treatments of acute stroke
- main criteria
  - time (delay) → IV thrombolysis
  - radiological (extent of hypodensity)
  - interindividual variability of the the kinetics of neuronal destruction (mismatch/collaterals) concept) → endovascular (mechanical) thrombectomy

Intravenous thrombolysis

EFFICACY OF IV THROMBOLYSIS ACCORDING TO TIME DELAY?
ANALYSE NINDS, ECASS II, ATLANTIS, EPITHET



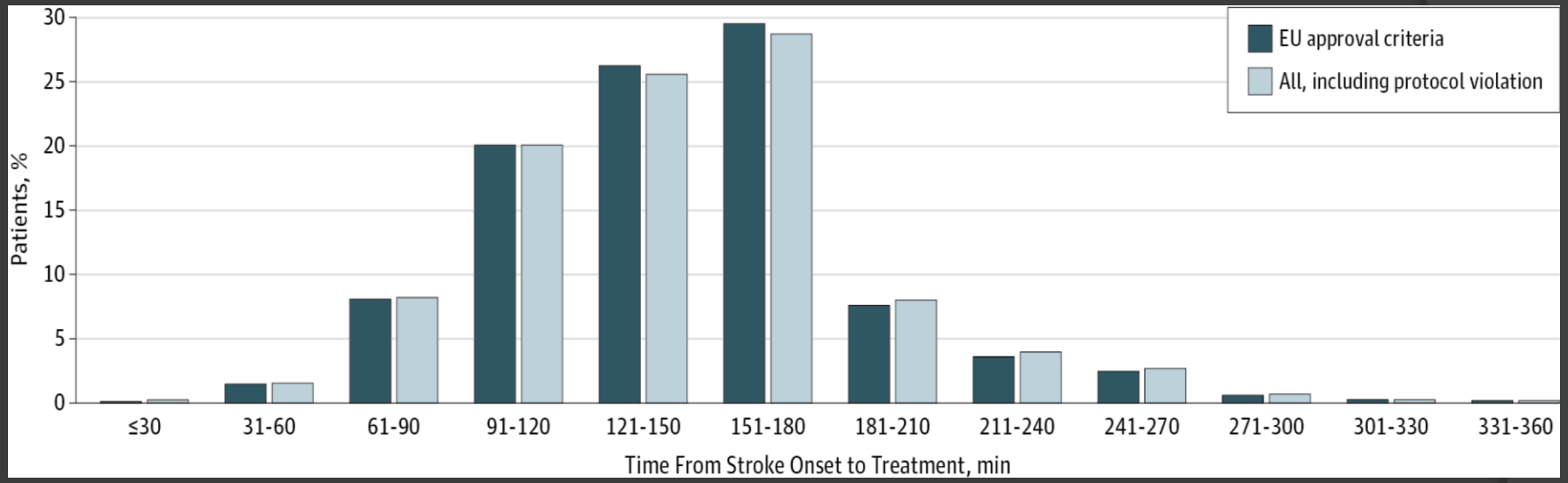
Lees K, Lancet 2010

Results of IV thromboysis
Data from international registry

- 29 618 patients with acute stroke
  - 283 (1.0%) treated within 4h30-6 hours
  - 4056 (13.7%) treated within 3h-4h30 hours
  - 25 279 (85.4%) treated within 3h hours

Niaz, JAMA Neurol. 2013

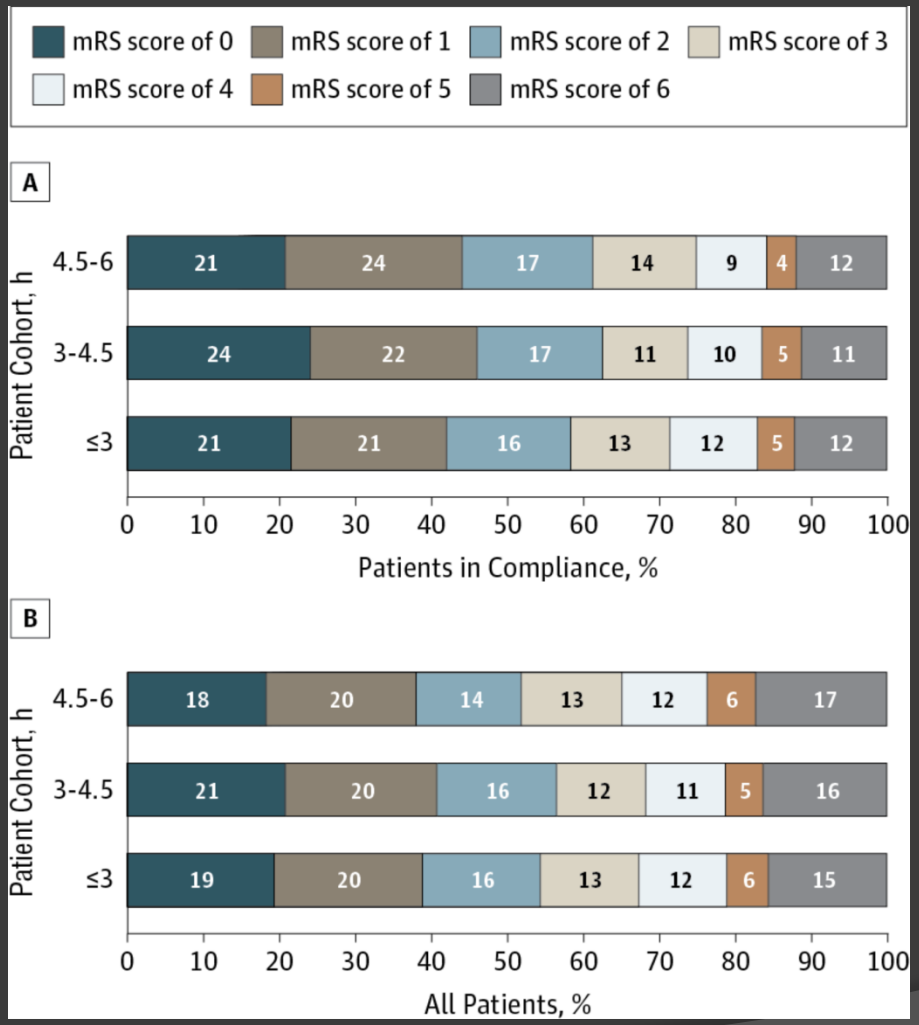
Results of IV thromboysis
Data from international registry



Proportion of patients according to 30 minutes interval since onset of symtoms

Niaz, JAMA Neurol. 2013

Results of IV thromboysis
Data from international registry



Patients treated in accordace with European criteria (A)

all patients treated (B)

Niaz, JAMA Neurol. 2013

Results of IV thromboysis
Data from international registry

Table 2. ICHs Detected by Computed Tomography or Magnetic Resonance Imaging on Any Posttreatment Imaging Scans[a]

Type of ICH	Within 4.5-6 h, No. (%) of Patients	*P* Value[b]	Within 3-4.5 h, No. (%) of Patients	Within 3 h, No. (%) of Patients	*P* Value[b]
Local					
None	223 (83.5)		3373 (86.8)	20 827 (84.6)	
Type 1 hemorrhagic infarct[c]	18 (6.7)		162 (4.2)	1356 (5.5)	
Type 2 hemorrhagic infarct[d]	9 (3.4)	.84	123 (3.2)	935 (3.8)	.001
Type 1 parenchymal ICH[e]	10 (3.8)		107 (2.8)	753 (3.1)	
Type 2 parenchymal ICH[f]	7 (2.6)		122 (3.1)	745 (3.0)	
Total	267 (100.0)		3887 (100.0)	24 616 (100.0)	
Remote					
None	264 (98.9)		3773 (97.1)	23 894 (97.1)	
Type 1 parenchymal ICH[g]	1 (0.37)	.18	71 (1.8)	451 (1.8)	.99
Type 2 parenchymal ICH[h]	2 (0.75)		42 (1.1)	265 (1.1)	
Total	267 (100.0)		3886 (100.0)	24 610 (100.0)	

Abbreviation: ICH, intracerebral hemorrhage.

[a] All patients were in compliance with European Union approval criteria.

[b] Patients treated within 4.5 to 6 hours or within 3 to 4.5 hours were compared with patients treated within 3 hours.

[c] Small petechiae along the margins of the infarct.

[d] More confluent petechiae within the infarct area but without space-occupying effect.

[e] Blood clot(s) not exceeding 30% of the infarct area with some mild space-occupying effect.

[f] Blood clots exceeding 30% of the infarct area with significant space-occupying effect.

[g] Small- or medium-sized blood clots located remote from the actual infarct; a mild space-occupying effect could be present.

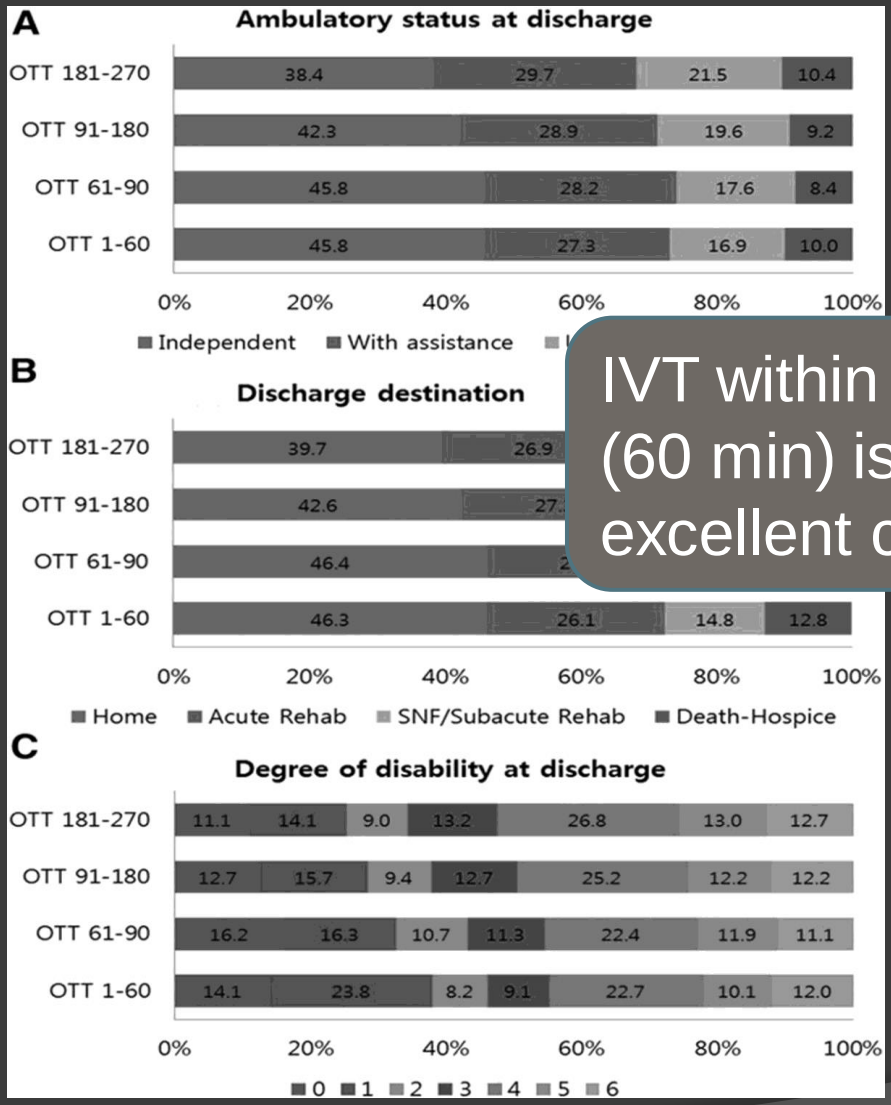
[h] Large confluent dense blood clots in an area remote from the actual infarct; significant space-occupying effect may be present.

Hemorrhagies detected by CT-scan or MRI

Niaz JAMA Neurol. 2016

FUNCTIONNAL PROGNOSIS ACCORDING TO TIME OF THROMBOLYSIS

>65 000 patients treated with IVT in the USA



IVT within the GOLDEN HOUR (60 min) is associated with an excellent clinical prognosis

Joon-Tae Kim, Circulation 2017

An important proportion of patients are still excluded from IVT

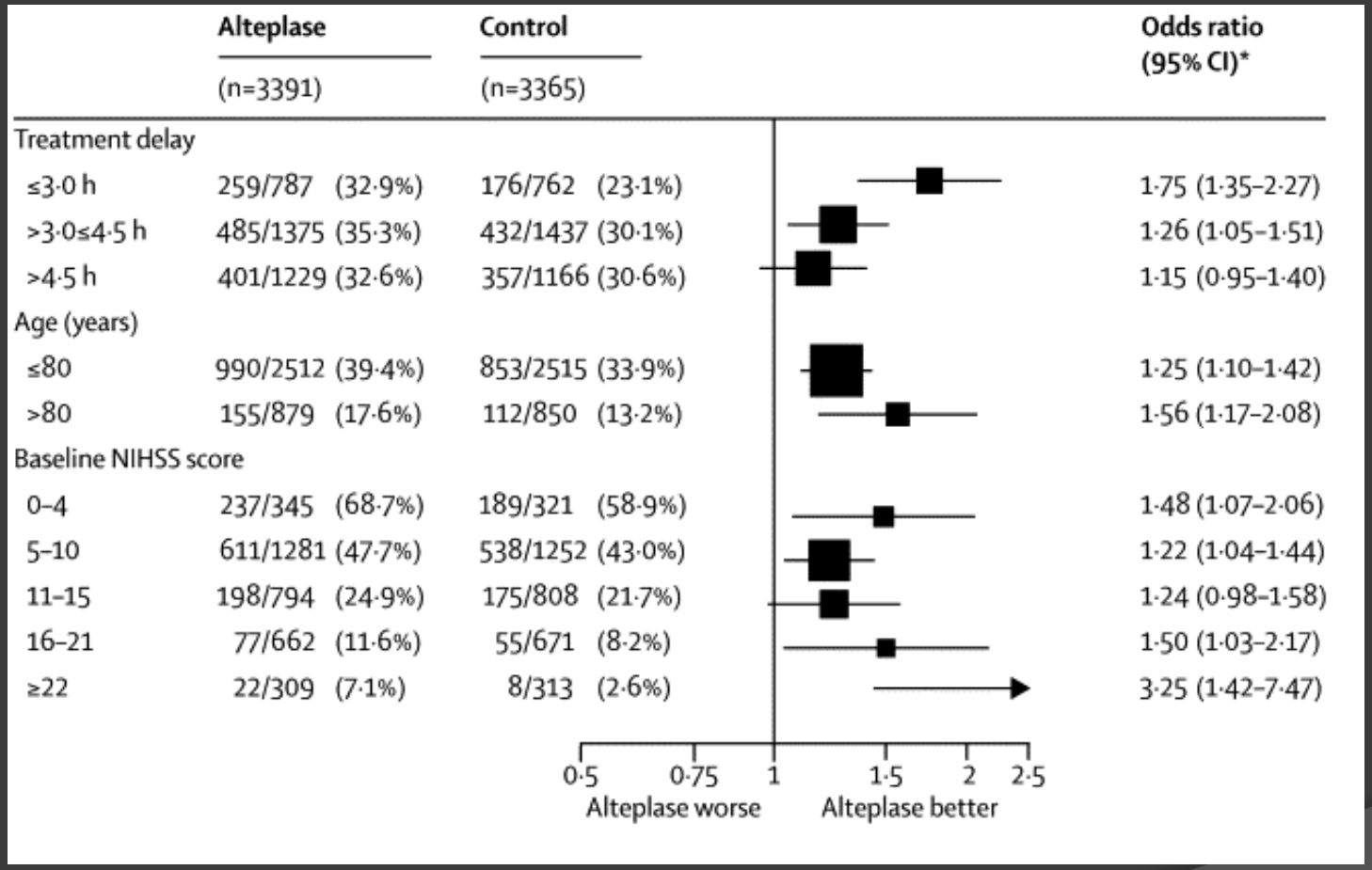
Multivariate analysis of reasons for non-thrombolysis comparing the first (n=959) with the second (n=1060) half of the observation period

Patients (n=2019)	2003–2006	2006–2011	OR	p Value	95% CI
Too late intravenous and no indication intra-arterial	127 (13%)	76 (7%)	1.79*	0.010	1.15 to 2.78
Unknown onset	268 (28%)	399 (38%)	0.69*	0.008	0.53 to 0.91
Too mild stroke	442 (46%)	497 (47%)	0.66*	0.002	0.51 to 0.86
Too severe stroke	20 (2%)	5 (1%)	10.56*	0.029	1.28 to 87.42
Rapid improvement to below threshold	16 (2%)	2 (0.2%)	5.43	0.109	0.69 to 43.01
Age >80 years	183 (19%)	102 (10%)	2.65*	0.000	1.76 to 3.99
Intracranial haemorrhage	3 (0.3%)	20 (2%)	0.11*	0.004	0.02 to 0.50
Other bleeding reasons	3 (0.3%)	21 (2%)	0.18*	0.020	0.04 to 0.77
Stroke uncertain	10 (1%)	48 (5%)	0.19*	0.000	0.08 to 0.44
Comorbidity/dependency	21 (2%)	64 (6%)	0.16*	0.000	0.09 to 0.31
Diabetes mellitus	132 (14%)	200 (19%)	0.53*	0.000	0.39 to 0.72
Hyperlipidaemia	589 (61%)	707 (67%)	0.53*	0.000	0.40 to 0.70
Probable atherosclerotic stroke mechanism (<50% stenosis)	151 (16%)	152 (14%)	1.50*	0.023	1.06 to 2.11
Microangiopathic stroke mechanism	171 (18%)	149 (14%)	1.72*	0.002	1.21 to 2.43

- **OR >1 means more likely in first half and <1 means more likely in second half of observation period.**
- **Asterisk (*), significant on p<0.05 level. Definitions of reasons for non-thrombolysis see text/table 5.**

Reiff T, Emerg Med J, 2017

Meta-analysis of 9 randomized studies (tPA vs Placebo) 6756 patients



Emberson, Lancet 2014

Intravenous thrombolysis in presence of rapid neurological improvement /or modest clinical deficit (NIH<5)

Austrian registry :

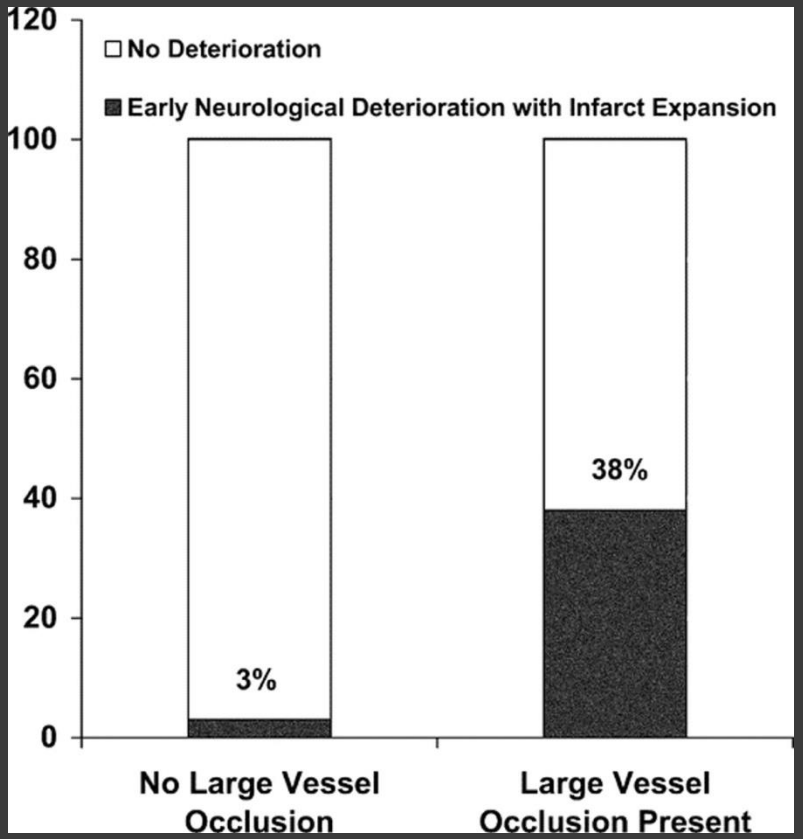
- Better prognosis for patients with mild deficit when treated with IV tPA (OR 1.49; IC 95%, 1.17-1.89; P<0.001) →NIH between 4-5
- NNT varies between 8 and14

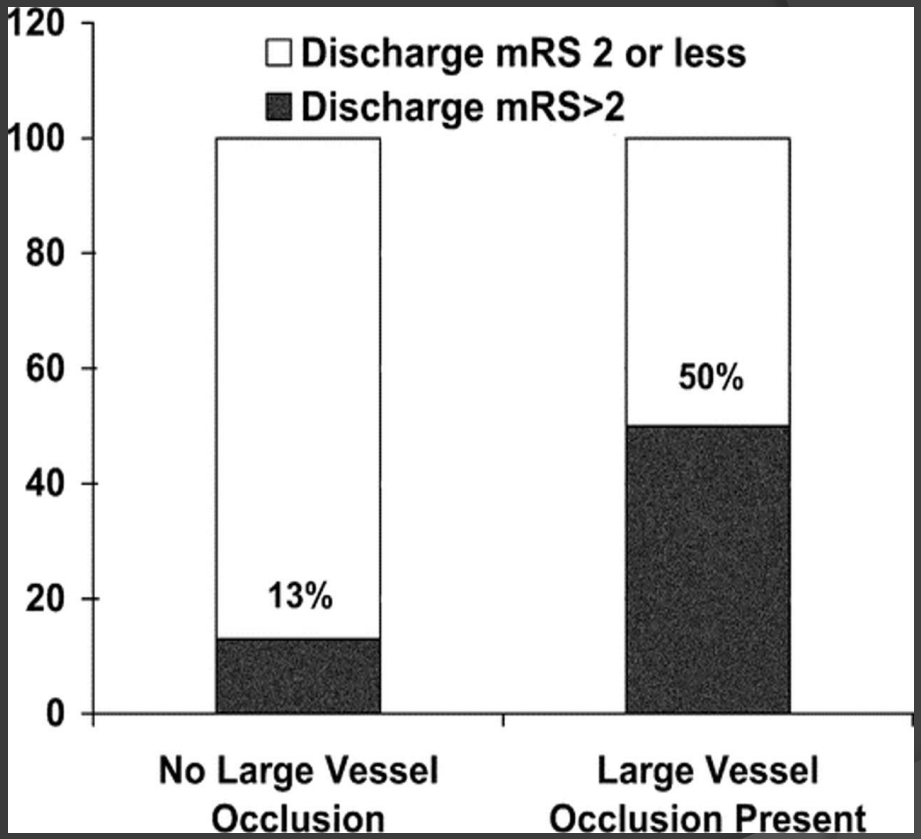
Monocentric prospective study:

10% of patients are excluded from thrombolysis because of too mild symptoms these patients may deteriorate during the first 24 h and have a bad prognosis at 3 months (20%)

Greisenegger S, Stroke 2014
Van Rajajee V, Neurology 2006

Patiens with NIHSS ≤4 or patients with more severe deficit but with rapid improvement





Van Rajajee, Neurology 2006

Wake up and unclear onset strokes

- an estimated 14% to 28% of ischemic strokes are wake-up strokes
- unclear-onset strokes are generally excluded from standard thrombolytic therapy

Kang DW, Int J Stroke, 2012

WAKE UP STROKE

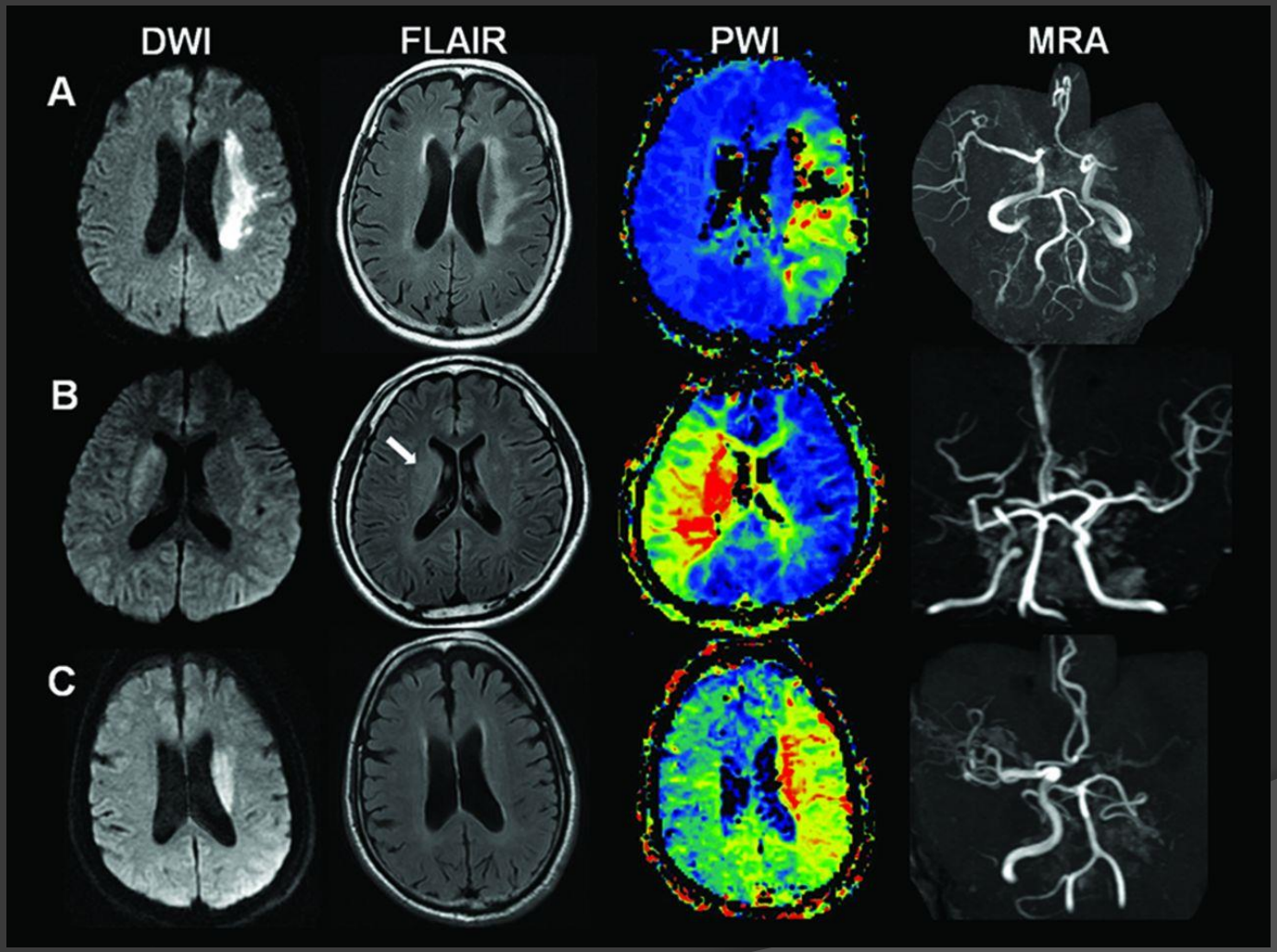
several studies of Wake-up stroke patients treated with IVT either with or without IAT

Table 3 Thrombolytic treatment of wake-up or unclear-onset strokes

	Author, year	Country	Study design	Imaging tool	Study period	Number of treated patients with wake-up or unclear-onset strokes	Mean age, years	Median NIHSS score	Imaging criteria	Time interval between first found abnormal time and treatment, hour	Thrombolysis drug, methods	mRS 0–1%	mRS 0–2%	SICH, %
1	Cho *et al.* 2008 (17)	Korea	Retrospective, three hospitals Including unclear-onset stroke	DWI/PWI	2004.3–2006.9	32	67·0	14·5	Perfusion (MTT)-diffusion mismatch >20% Infarct volume on DWI <50% of MCA territory DWI–FLAIR mismatch (+)	6	tPA IV, IV/IA, or IA	37·5	50·0	6·3
2	Adams *et al.* 2008 (5)	International	Randomized, double-blind placebo-controlled international trial (119 hospitals)	CT	2003.12–2005.9	22	68·6	10	Infarct volume <50% of MCA territory	3	Abciximab IV	10·0	33·0	13·6
3	Barreto *et al.* 2009 (6)	United States	Retrospective, single center database	CT	2003.3–2008.1	46	62·0	16	Infarct volume <1/3 of MCA territory	3	tPA IV, IV/IA, or IA	14·0	28·0	4·3
4	Breuer *et al.* 2010 (12)	Germany	Retrospective, single center database	CT/MRI	2006.10–2008.5	10	73 (median)	10·5	PWI/DWI mismatch (+) DWI lesion <33% of MCA territory DWI–FLAIR mismatch (+)	6	tPA IV	30·0	50·0	0
5	Kuruvilla *et al.* 2010 (7)	United States	Case report	CT/DSA	-	2	41 and 25	13 and 19	-	-	tPA IA + clot retrieval/clot retrieval + balloon angioplasty + tPA IA	100	100	0
6	Kim *et al.* 2011 (47)	Korea	Retrospective, single center database Including wake-up and unclear-onset strokes	CT/DWI/PWI	2008.9–2010.2	29	66·9	13	Early infarct signs at <1/3 of MCA territory on CT Catheter-accessible MCA or distal ICA on MRA Small DWI lesions (<1/3 of MCA territory) A large MTT delay in PWI by visual inspection	3	tPA IV, tPA IV/IA urokinase	27·6	44·8	10·3
7	Aoki *et al.* 2011 (48)	Japan	Prospective, single center	DWI/FLAIR	2009.6–2010.5	10	84 (median)	14	Presence of occlusion (ICA, M1 or M2) on MRA No large infarcts on DWI (large infarct: ASPECTS ≤5) DWI/FLAIR mismatch (+)	3	tPA IV	30·0	40·0	0
8	Kang *et al.* 2011 (46)	Korea	Prospective, multicenter (six hospitals)	DWI/PWI	2006.9–2009.6	83	67 (median)	14	Perfusion (MTT)-diffusion mismatch > 20% Infarct volume on DWI <1/3 of MCA territory DWI–FLAIR mismatch (+)	6	tPA IV, IV/IA, IA or angioplasty/ stenting	28·9	43·2	6·0

NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin scale; SICH, symptomatic intracerebral hemorrhage; DWI, diffusion-weighted imaging; PWI, perfusion-weighted imaging; MTT, mean transit time; MCA, middle cerebral artery; FLAIR, fluid-attenuated inversion recovery; tPA, tissue plasminogen activator; IV, intravenous; IA, intra-arterial; CT, computed tomography; MRI, magnetic resonance imaging; DSA, digital subtraction angiography; MRA, magnetic resonance angiography; ASPECTS, Alberta Stroke Program Early CT Score; ICA, internal cerebral artery.

DIFFUSION –FLAIR MISMATCH AND PERFUSION-DIFFUSION MISMATCH.



Dong-Wha Kang et al. Stroke. 2012

Endovascular therapy

Recanalization and reperfusion therapies of acute ischemic stroke: the past limitations

- futile recanalization occurs when successful recanalization fails to improve functional outcome:
  - In 2013, 3 publications reported neutral results of three randomized studies comparing endovascular therapy with or without IV thrombolysis therapy:
  - SYNTHESIS
  - Interventional Management of Stroke (IMS) III
  - Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE)

Recanalization and reperfusion therapies of acute ischemic stroke: the past limitations

- these trials were not adequately designed to prove the superiority of endovascular treatment because:
  - did not use optimal target populations
  - vascular status was not evaluated in all patients
  - high rates of patients did not have enough mismatch (Mr Rescue only 58% favourable penumbral pattern)
  - time from baseline neuroimaging to recanalization were too long (Mr Rescue up 330 min)
  - devices used were obsolete relative to stent-retrievers

Davalos , Front Neurol 2014

Recanalization and reperfusion therapies of acute ischemic stroke: subsequent studies all improved

- delays from imaging to recanalization shortened
- most of the patients included with a favourable penumbral/collateral pattern
- vascular status was predefined
- stent retriever devices used

5 RCT published in 2015 and including overall 1287 patients

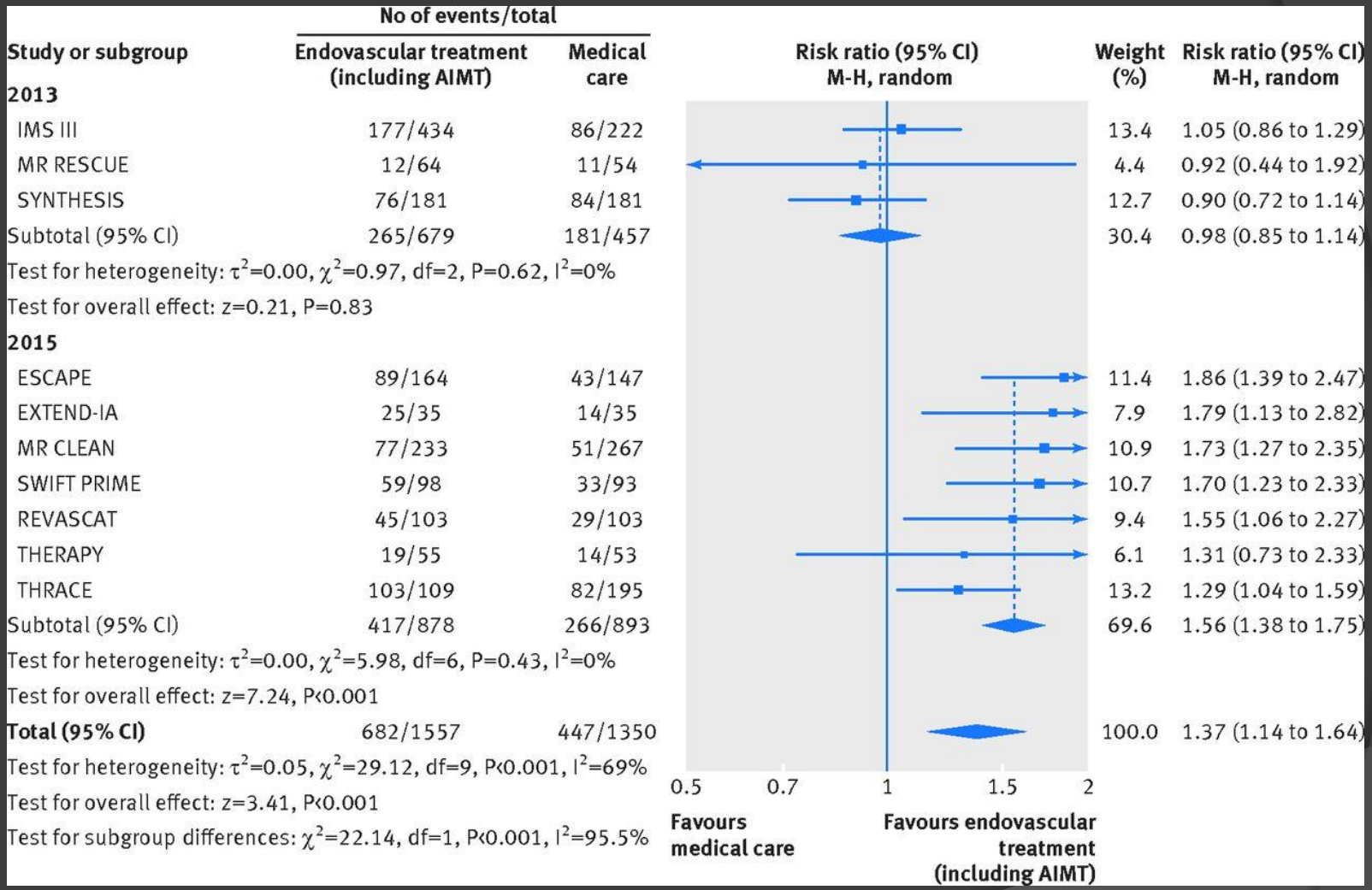
- Mr Clean (6h)
- ESCAPE (12h)
- EXTEND IA (6h)
- SWIFT(8h)
- REVASCAT (8h)

Endovascular treatment versus medical care alone for ischaemic stroke: systematic review and meta-analysis: 10 randomised controlled trials (n=2925)

- pooled analysis endovascular treatment was associated with a higher proportion of patients experiencing good (mRS ≤2) and excellent (scores ≤1) outcomes 90 days after stroke compared to medical care including IVT
- In most of these studies, more than 86% of the patients were treated with stent retrievers, and rates of recanalisation were higher (>58%) than previously reported

Filipe Brogueira Rodrigues, BMJ 2016

Forest plot for a good functional outcome (modified Rankin scale core ≤2) at 90 days, including subgroup analysis by year of study publication.



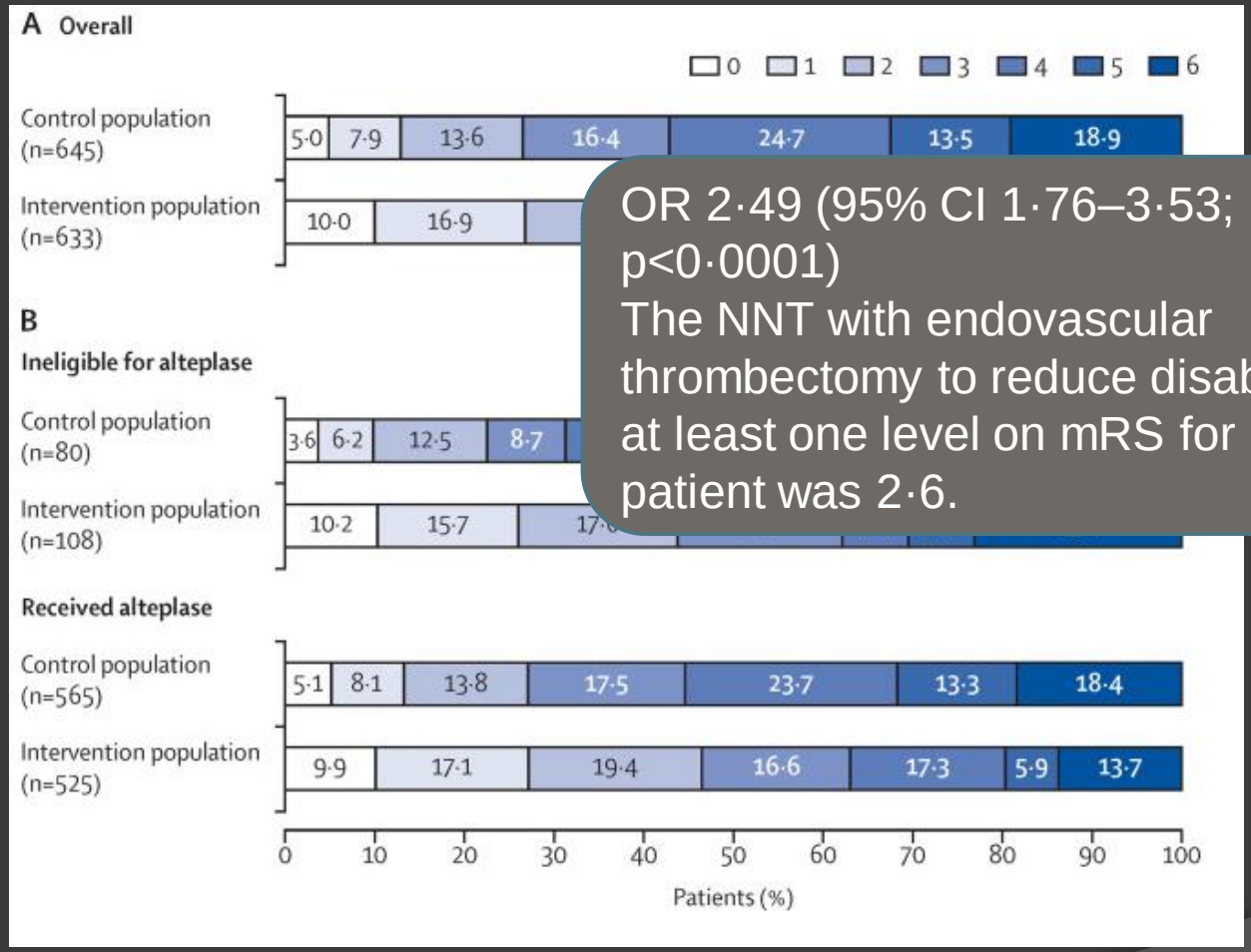
Study or subgroup	No of events/total: Endovascular treatment (including AIMT)	No of events/total: Medical care	Weight (%)	Risk ratio (95% CI) M-H, random
2013				
IMS III	177/434	86/222	13.4	1.05 (0.86 to 1.29)
MR RESCUE	12/64	11/54	4.4	0.92 (0.44 to 1.92)
SYNTHESIS	76/181	84/181	12.7	0.90 (0.72 to 1.14)
Subtotal (95% CI)	265/679	181/457	30.4	0.98 (0.85 to 1.14)
Test for heterogeneity: τ^2=0.00, χ^2=0.97, df=2, P=0.62, I^2=0%				
Test for overall effect: z=0.21, P=0.83				
2015				
ESCAPE	89/164	43/147	11.4	1.86 (1.39 to 2.47)
EXTEND-IA	25/35	14/35	7.9	1.79 (1.13 to 2.82)
MR CLEAN	77/233	51/267	10.9	1.73 (1.27 to 2.35)
SWIFT PRIME	59/98	33/93	10.7	1.70 (1.23 to 2.33)
REVASCAT	45/103	29/103	9.4	1.55 (1.06 to 2.27)
THERAPY	19/55	14/53	6.1	1.31 (0.73 to 2.33)
THRACE	103/109	82/195	13.2	1.29 (1.04 to 1.59)
Subtotal (95% CI)	417/878	266/893	69.6	1.56 (1.38 to 1.75)
Test for heterogeneity: τ^2=0.00, χ^2=5.98, df=6, P=0.43, I^2=0%				
Test for overall effect: z=7.24, P<0.001				
Total (95% CI)	682/1557	447/1350	100.0	1.37 (1.14 to 1.64)
Test for heterogeneity: τ^2=0.05, χ^2=29.12, df=9, P<0.001, I^2=69%				
Test for overall effect: z=3.41, P<0.001				
Test for subgroup differences: χ^2=22.14, df=1, P<0.001, I^2=95.5%				

Filipe Brogueira Rodrigues et al. BMJ 2016

Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials

- HERMES collaboration to pool patient-level data from five trials (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA)
- occlusion of the proximal anterior artery circulation (distal ICA, M1, M2)
  - randomly assigned to receive either endovascular thrombectomy within 12 h of symptom onset or standard care (control),
  - with a primary outcome of reduced disability on the modified Rankin Scale (mRS) at 90 days.

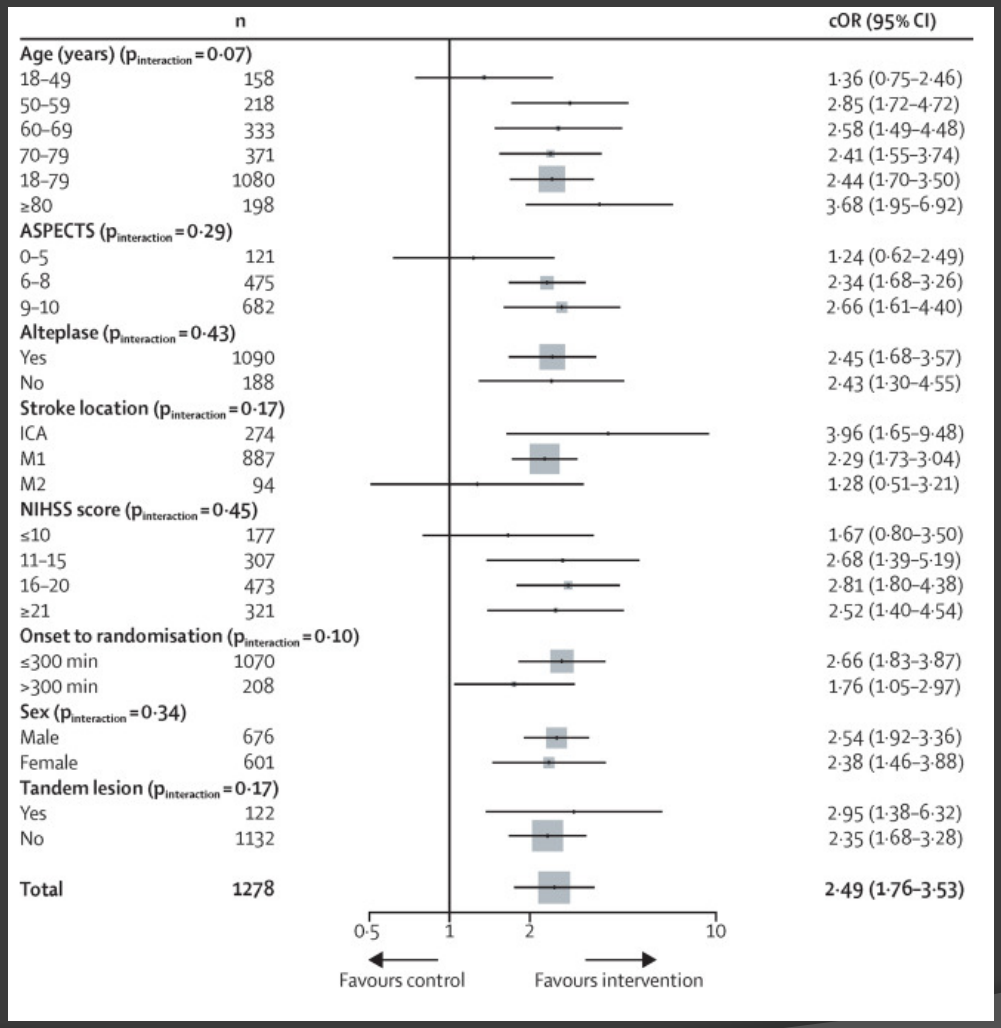
Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trialsEndovascular thrombectomy



OR 2·49 (95% CI 1·76–3·53; p<0·0001)
The NNT with endovascular thrombectomy to reduce disability by at least one level on mRS for one patient was 2·6.

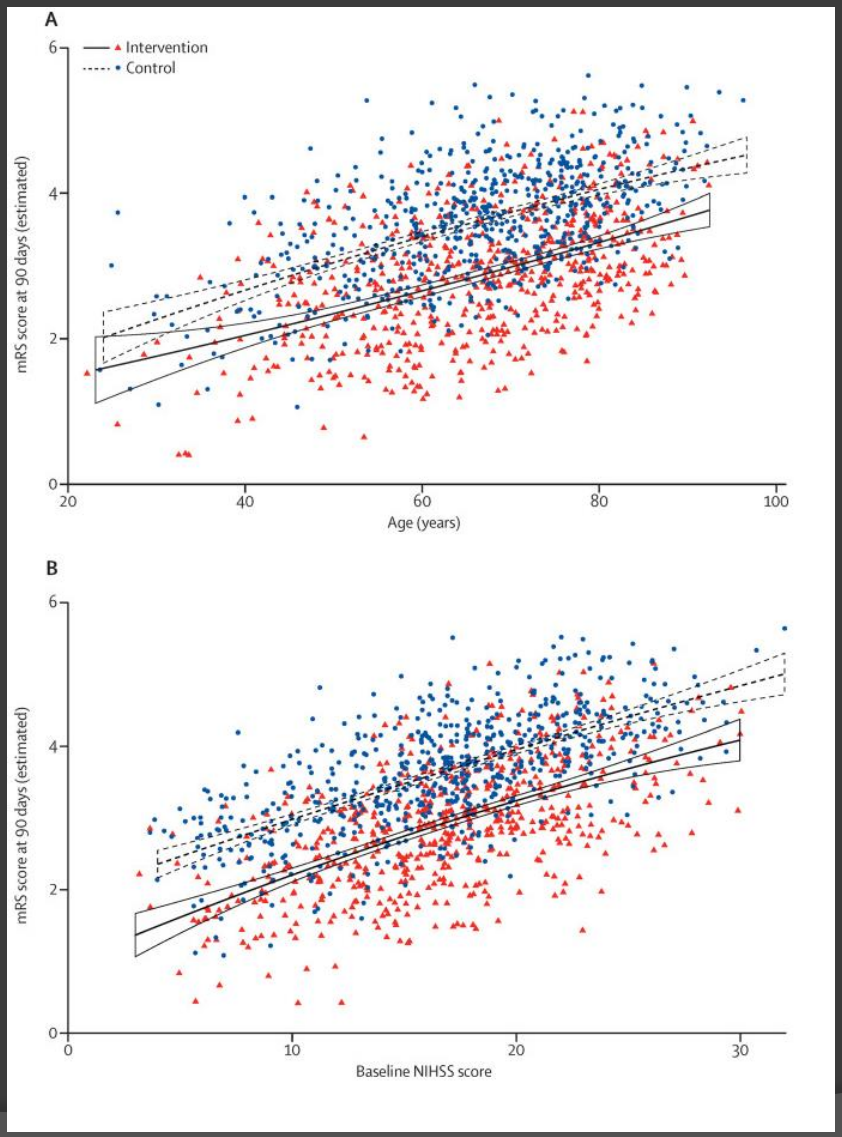
Muir K, Lancet 2015

Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trialsEndovascular thrombectomy



Muir K, Lancet 2015

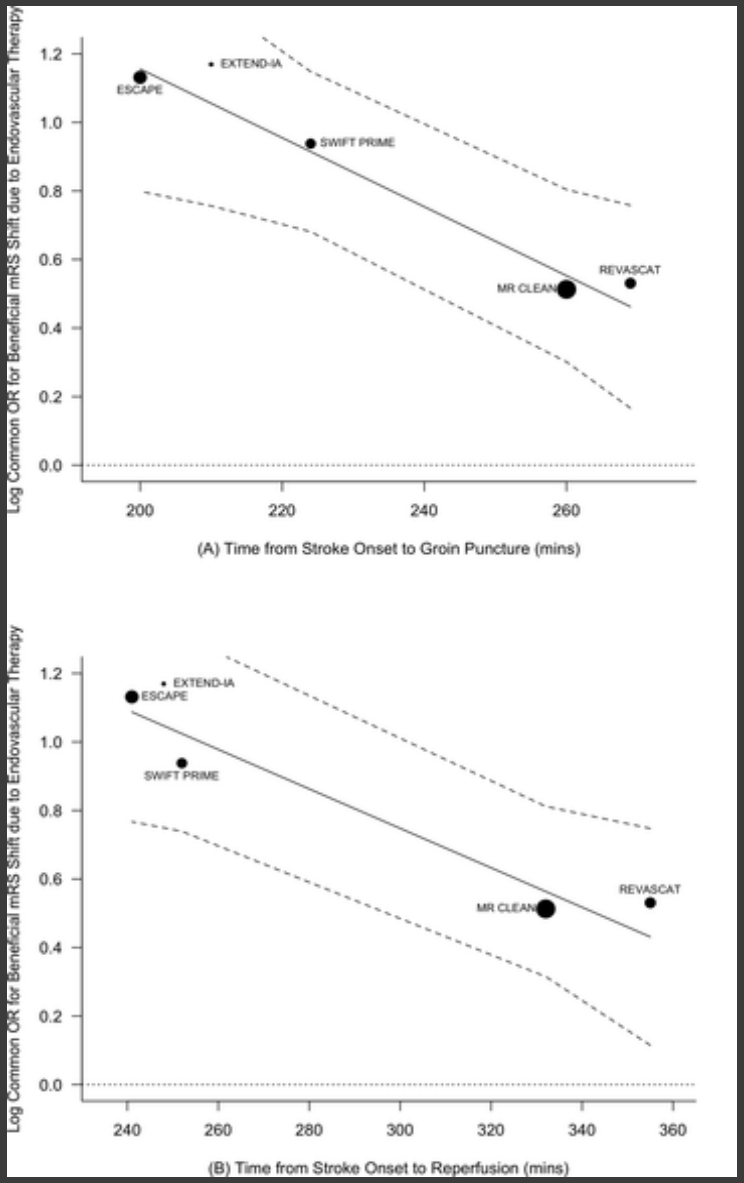
Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomisedtrials Endovascular thrombectomy



mRS score at 90 days estimated with a mixed methods linear regression versus age (A) and baseline NIHSS (B)

Muir K, Lancet 2015

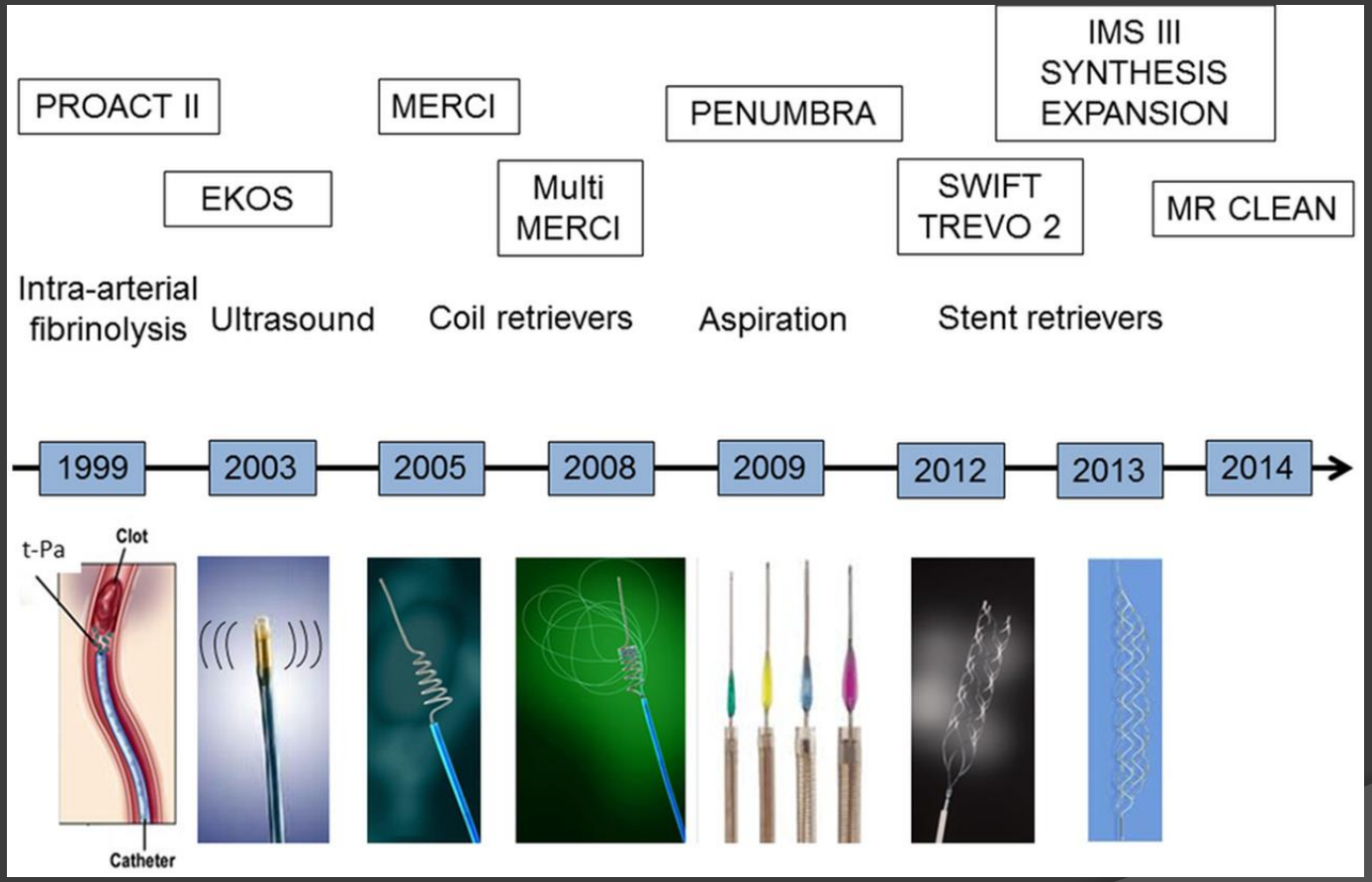
EFFICACITY ACCORDING TO DELAY



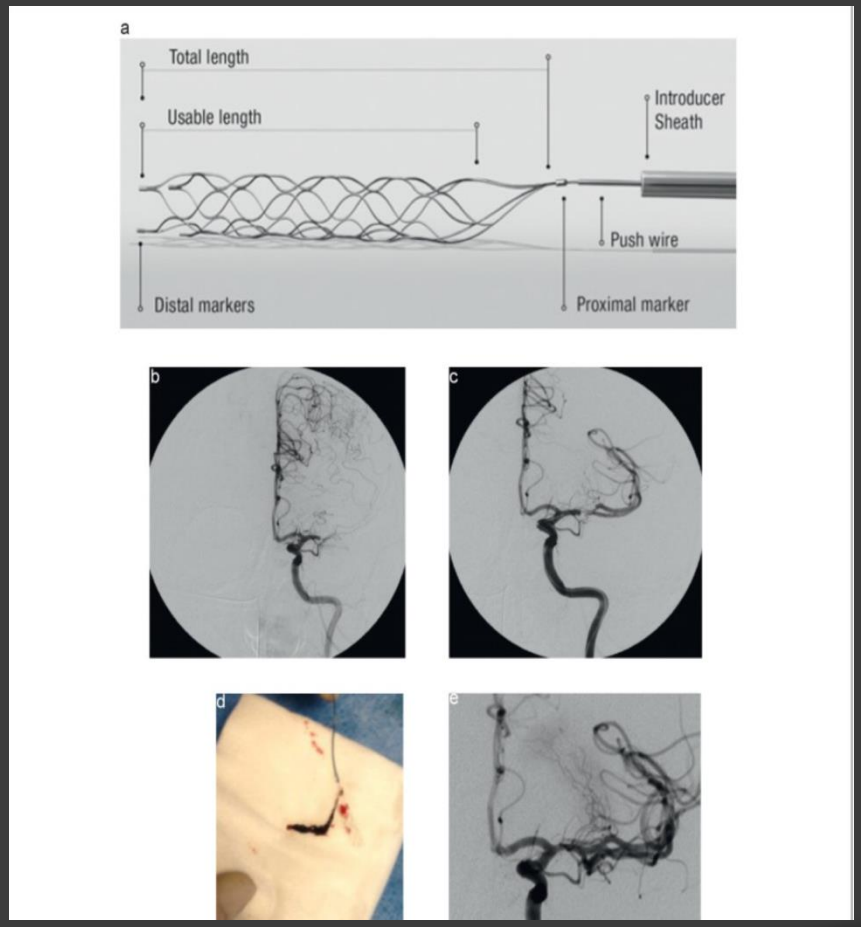
Delay between onset of symtoms, groin puncture and recanalisation is associated with clinical prognosis (respectively p=0.007 and p=0.0089)

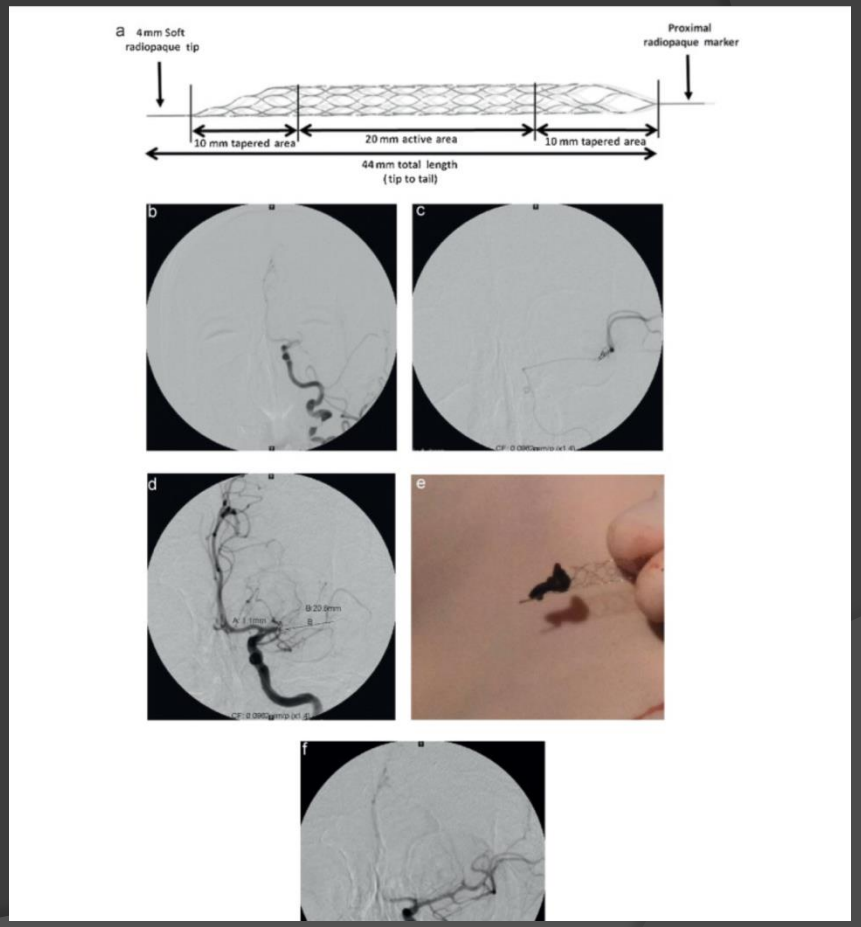
Bush CK, Plos one, 2016

ENDOVASCULAR TREATMENT AND DIFFERENT DEVICES

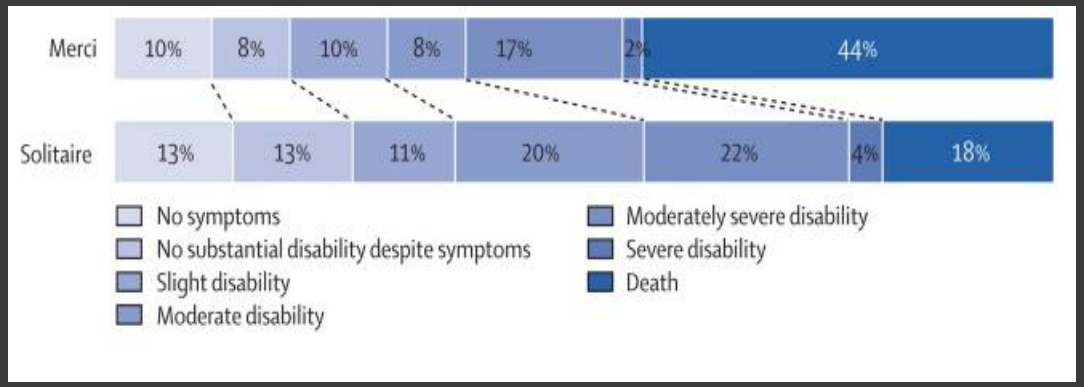


SOLITAIRE AND TREVO RETRIEVER

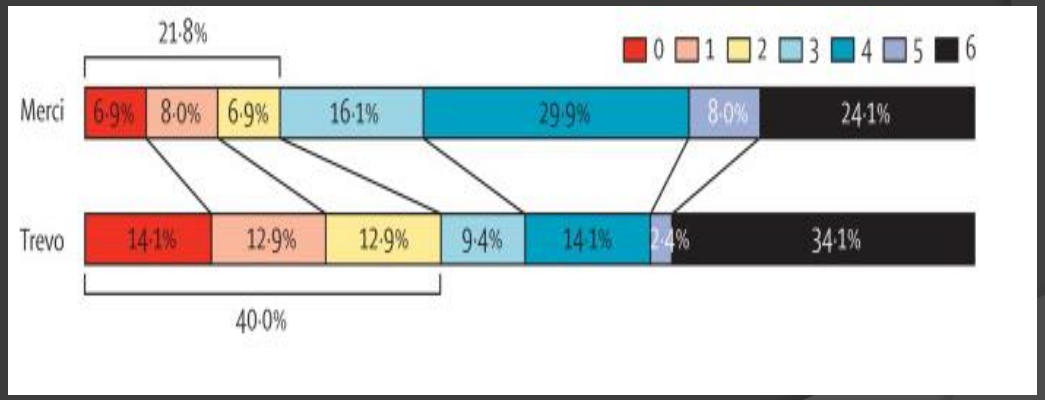




Solitaire flow restoration device (n=58) versus the Merci Retriever (n=55) in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial



Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial



The Solitaire Flow Restoration Device achieved substantially better angiographic, safety, and clinical outcomes than did the Merci Retrieval System.

Saver, Lancet 2012
Nogueira RG, Lancet 2012

Recanalisation in 76 (86%) patients in the Trevo group and 54 (60%) in the Merci group (OR 4·22, 95% CI 1·92–9·69; $p_{superiority}$<0·0001).

Comparing different thrombectomy techniques in five large-volume centers: a 'real world' observational study

- **R**etrospective study of 450 patients with occlusion of the anterior circulation, treated in five high-volume centers from 2013 to 2016
- The treatment techniques were divided in three categories: first-pass use of a large-bore aspiration-catheter; first-pass use of a stent-retriever; and primary combined approach (PCA) of an aspiration-catheter and stent-retriever

Comparing different thrombectomy techniques in five large-volume centers: a 'real world' observational study

Table 2
Results of the primary multiple logistic regression analysis for the 'successful reperfusion' in the ITT population

	Comparison	OR	95% CI (OR)	pvalue
Technique	Global	–	–	<0.01
	PCA versus aspiration	2.53	1.45 to 4.43	<0.01
	PCA versus stent-retriever	3.48	1.92 to 6.32	<0.01
	Aspiration versus stent-retriever	1.38	0.80 to 2.36	0.19
Age	Per year	1.01	0.99 to 1.03	0.48
Sex	Male versus female	1.07	0.68 to; 1.71	0.76
Hypertension	No versus. yes	1.15	0.66 to 2.00	0.62

- significantly higher reperfusion rates, with 86% of successful reperfusion in the PCA-group compared with 73% in the aspiration group and 65% in the stent-retriever group.
- there was no significant difference in groin to reperfusion time.
- Lowest Emboli rates and attempts were reported with the combined approach

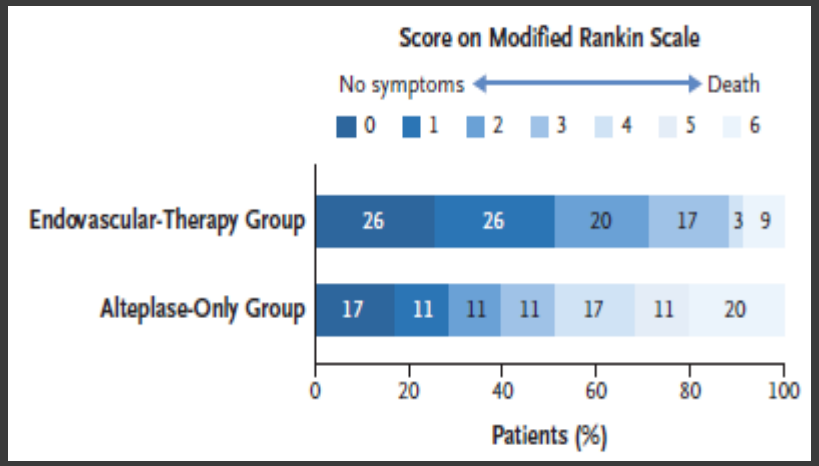
Hesse, Neurointerv Surg, 2017

Use of imaging criteria to select patients

Use of imaging criteria to select patients

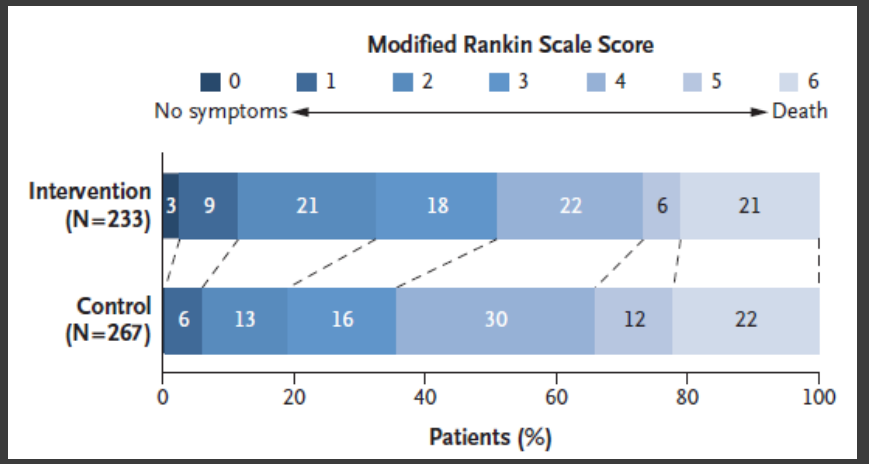
- All 5 studies prespecified proximal occlusion as inclusion criteria. In majority of cases, this was performed with CTA
- Mr Clean (6h): ASPECTS score
- ESCAPE (12h): CT-Angio (multiphase) collaterals evaluation
- EXTEND IA (6h): CT perfusion and presence of mismatch and core <70 ml
- SWIFT: use of RAPID for mismatch assessment, patients with core >70ml were excluded
- REVASCAT(8h): ASPECTS score

COMPARISON WITH AND WITHOUT PERFUSION IMAGING SELECTION



Median time from stroke onset to groin puncture: 210 min

EXTEND IA



Median Time from stroke onset to groin puncture : 260 min

MR CLEAN

Campbell, New Engl J of Med, 2015
Berkhemer ,New Engl J of Med, 2015

Imaging of site of occlusion, perfusion or collaterals in the 5 randomised studies

post-hoc analysis of Mr Clean trial

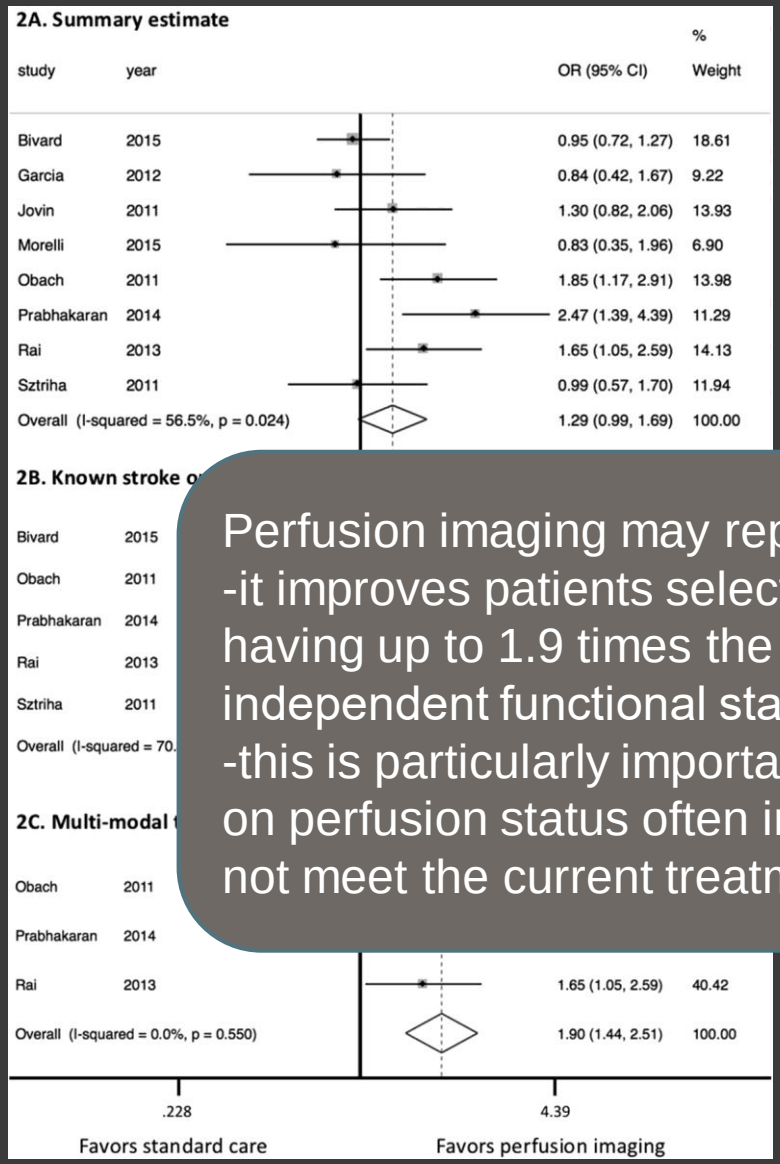
- There was a significant modification of treatment effect by collaterals (P=0.038).
- The strongest benefit (OR odds 3.2, 95% CI 1.7-6.2]) was found in patients with good collaterals (grade 3)
- OR was 1.6, 95% CI 1.0-2.7, for moderate collaterals (grade 2),
- OR 1.2, 95% CI 0.7-2.3, for poor collaterals (grade 1)
- OR 1.0 , 95% CI 0.1-8.7, for patients with absent collaterals (grade 0).

Berkhemer OA, Stroke 2016

Usefulness of perfusion imaging in acute stroke treatment: a systematic review and meta-analysis

- 994 patients were treated with the aid of perfusion imaging compared with 1819 patients treated with standard care.

Riu, Neuroimaging, 2016



Perfusion imaging may represent a complementary tool:
-it improves patients selection with a subset of patients having up to 1.9 times the odds of achieving independent functional status at 3 months
-this is particularly important as patients selected based on perfusion status often included individuals who did not meet the current treatment eligibility criteria

A. Of the patients who were treated with adjunctive perfusion imaging, 51.1% experienced a favorable clinical outcome at 3-month follow-up compared with 45.6% of patients who were treated with

on studies that
e there was a
e outcome in the
CI 1.08 to 1.57;
ysis of studies
n or unclear
mes between the
to 1.53; p=0.66).

C. Studies that used multimodal therapy showed the largest effect size, favoring perfusion imaging (OR 1.89, 95% CI 1.44 to 2.51; p<0.01).

Riu, Neuroimaging, 2016

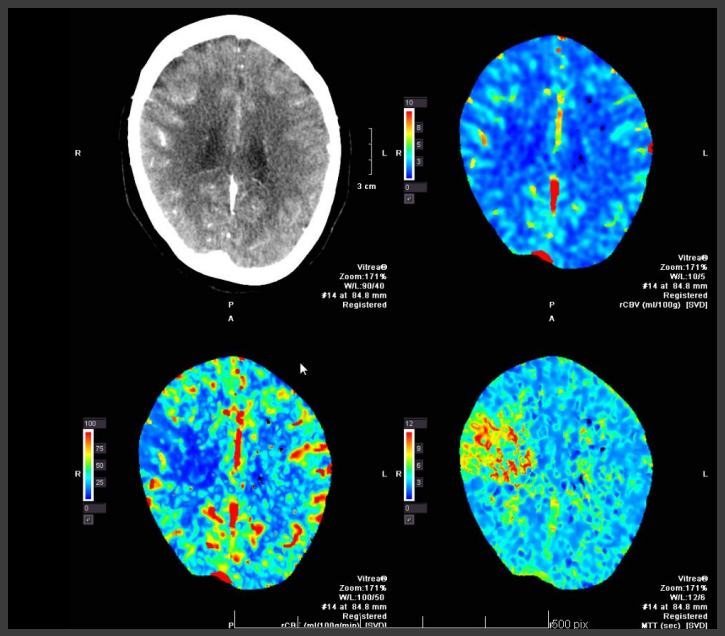
Mechanical Thrombectomy for Minor and Mild Stroke

Is Reperfusion Useful in Ischaemic Stroke Patients Presenting with a Low National Institutes of Health Stroke Scale and a Proximal Large vessel Occlusion of the Anterior Circulation?

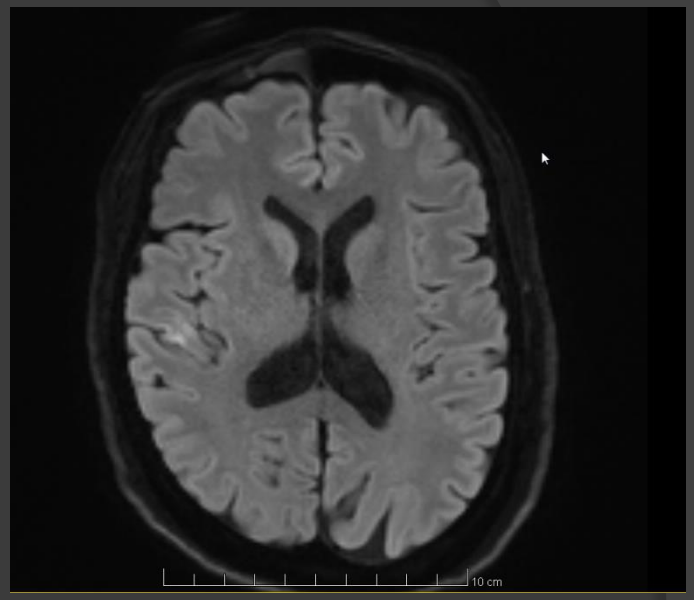
- patients presenting with minor or mild stroke symptoms represent about two-thirds of stroke patients
- almost one-third of these patients are unable to ambulate independently at the time of discharge

Dargazanli, Cerebrovasc Dis 2017

66 years old man presenting with dysarthria and mild weakness of the left arm



NIHSS is 3 at baseline and then 10 at the end of IV thrombolysis



M2 occlusion (superior branch)

Final MRI

Mechanical Thrombectomy for Minor and Mild Stroke Patients Harboring Large Vessel Occlusion in the Anterior Circulation: A Multicenter Cohort Study.

- Multicenter cohort study involving 4 comprehensive stroke centers having 2 therapeutic approaches:
  - urgent thrombectomy associated with best medical treatment versus BMT first and MT if worsening occurs

Dargazanli,Stroke 2017

Mechanical Thrombectomy for Minor and Mild Stroke Patients Harboring Large Vessel Occlusion in the Anterior Circulation: A Multicenter Cohort Study.

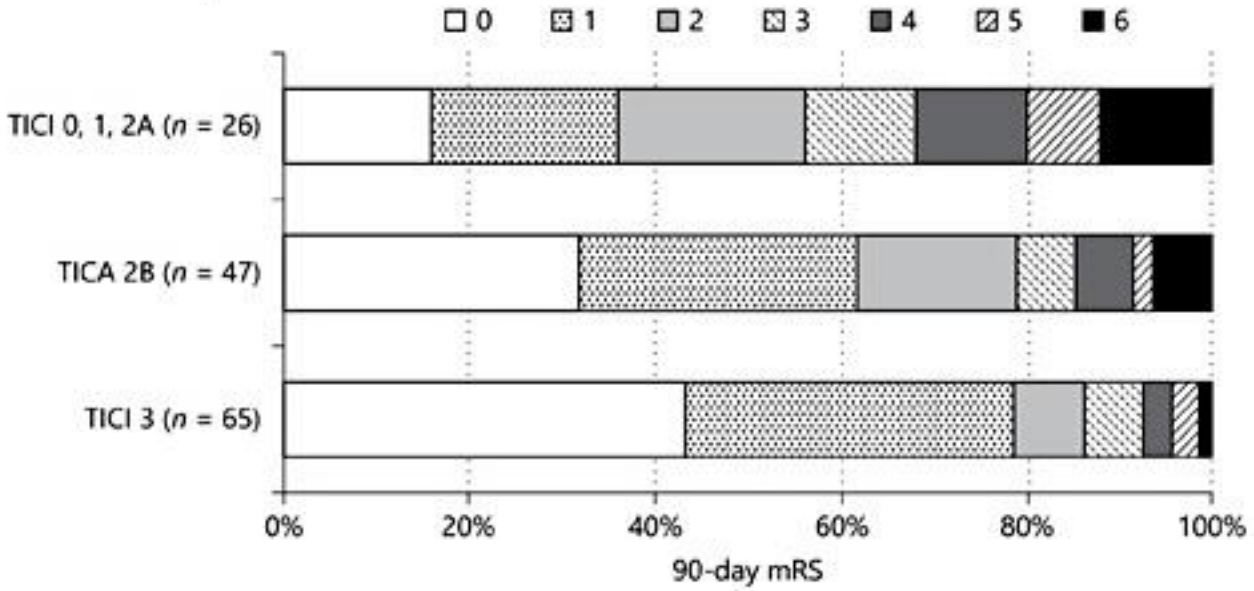
- 301 patients were included
  - 170 with urgent MT associated with BMT
  - 131 with BMT alone as first-line treatment
  - 24 patients (18.0%) in the medical group had rescue MT because of neurological worsening.
  - excellent outcome was achieved in 64.5% of patients, with no difference between the 2 groups

Dargazanli,Stroke 2017

Is Reperfusion Useful in Ischaemic Stroke Patients Presenting with a Low National Institutes of Health Stroke Scale and a Proximal Large Vessel Occlusion of the Anterior Circulation?

138 consecutive patients with acute LVO of the anterior circulation

Distribution of modified Rankin Score (mRs) at 90 Days according to reperfusion status ($p < 0.001$). Thrombolys in cerebral infarction (TICI) scores of 0, 1, 2A indicate a failed/poor reperfusion. TICI scores of 2B, 3 indicate a successful reperfusion.



Dargazanli, Cerebrovasc Dis 2017

Is there still a need for IV thrombolysis in patients with proximal occlusions

Intravenous Thrombolysis Facilitates Successful Recanalization with Stent-Retriever Mechanical Thrombectomy in Middle Cerebral Artery Occlusions

- retrospective study investigated whether concomitant IVT influences the revascularization efficacy in mechanical thrombectomy (MT)
  - 93 patients who presented with an occlusion of the middle cerebral artery (MCA): of these patients, 66 (71%) received IVT
  - rate of successful recanalizations (TICI≥ 2b) was significantly higher in patients with MCA occlusion and concomitant IVT ($P = .01$)
  - Stepwise logistic regression identified IVT and thrombus length as predictive factors for successful mechanical recanalization ($P = .004$, $P = .002$).

Behme, J of Stroke and Cerebrovasc Dis 2016

Prior IV Thrombolysis Facilitates Mechanical Thrombectomy in Acute Ischemic Stroke

Presented at European Stroke Conference, Nice, 2014

- Comparison in consecutively recruited patients either eligible for MET alone (intravenous fibrinolysis contraindication) or receiving MET preceded by IVT for proximal middle cerebral artery (MCA) occlusion within 6 hours of stroke onset:
  - the duration of the procedure
  - number of passes
  - recanalization rate
  - safety issues
  - outcome

Guedin, J Stroke and Cerebrovasc Dis, 2015

Prior IV Thrombolysis Facilitates Mechanical Thrombectomy in Acute Ischemic Stroke

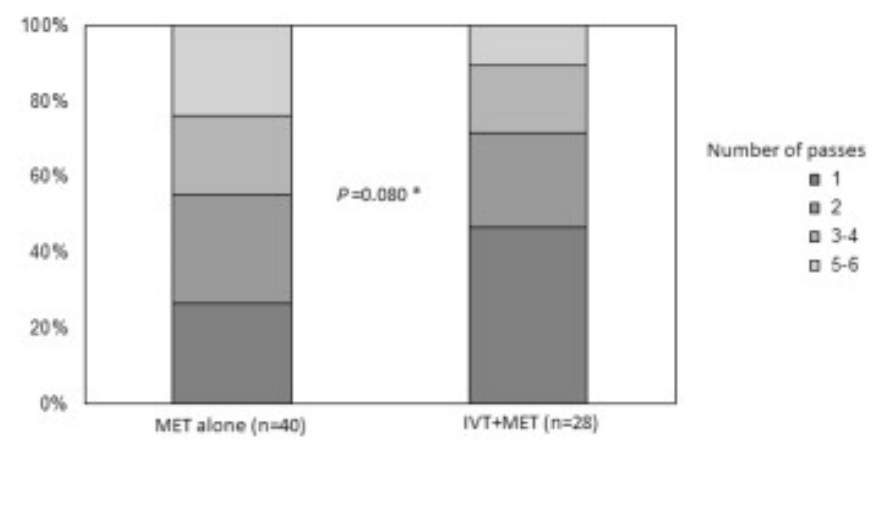
Presented at European Stroke Conference, Nice, 2014

- 68 cases with proximal MCA occlusion were available for analysis (MET alone, 40; IVT + MET, 28)
  - median duration of the endovascular procedure (from groin puncture to recanalization) was significantly shorter in the IVT + MET group compared with that in MET alone (35 minutes [21-60] versus 60 minutes [25-91]; *P* = .043).
  - The number of passes of the thrombectomy device per patient tended to be lower in the IVT + MET group than those in the MET group (*P* = .080)
  - The IVT + MET group also had a higher rate of complete recanalization and a better outcome at 3 months

Guedin, J Stroke and Cerebrovasc Dis, 2015

Prior IV Thrombolysis Facilitates Mechanical Thrombectomy in Acute Ischemic Stroke

Presented at European Stroke Conference, Nice, 2014



Number of passes of the thrombectomy device according to prior use of intravenous thrombolysis. **P* value for the comparison in number of passes was calculated using the Mann–Whitney *U* test (before categorization done for the presentation). Abbreviations: IVT, intravenous thrombolysis; MET, mechanical endovascular therapy.

Guedin, J Stroke and Cerebrovasc Dis, 2015

Mechanical Thrombectomy Outcomes With and Without Intravenous Thrombolysis in Stroke Patients: a meta-analysis

- 13 studies to determine whether:
  - functional outcome at 90 days successful
  - recanalization rate
  - symptomatic intracerebral hemorrhage rate → differed between patients who underwent mechanical thrombectomy with (MT+IVT) and without (MT−IVT) pre-treatment with intravenous thrombolysis.

Mistry Stroke 2017

Mechanical Thrombectomy Outcomes With and Without Intravenous Thrombolysis in Stroke Patients: a meta-analysis

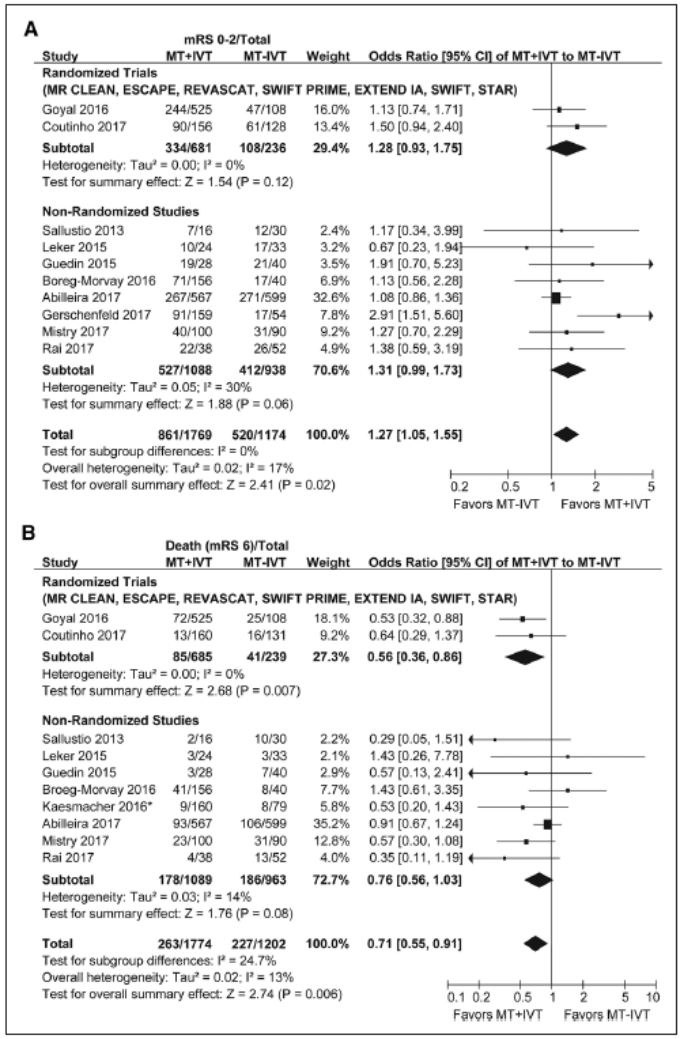


Figure 1. Meta-analyses of studies comparing good functional outcomes (modified Rankin Scale [mRS] score of 0–2, **A**) and mortality (mRS 6; **B**) at 90 days in patients who underwent mechanical thrombectomy with (MT+IVT) and without pre-treatment with intravenous thrombolysis (MT-IVT). *Reported only in-hospital mortality. CI indicates confidence interval.

Mistry Stroke 2017

Mechanical Thrombectomy Outcomes With and Without Intravenous Thrombolysis in Stroke Patients: a meta-analysis

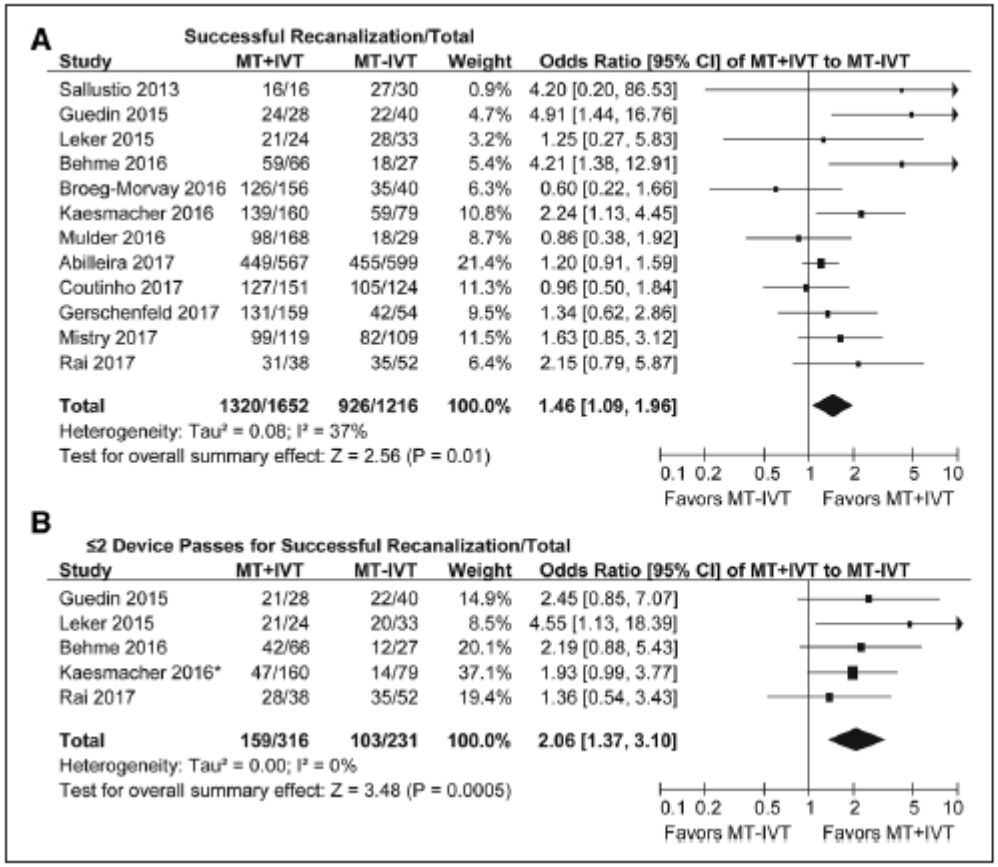


Figure 4. Meta-analyses of studies comparing rates of successful recanalization (**A**) and number of patients that required ≤2 passes of a device to achieve it (**B**) in patients who underwent mechanical thrombectomy with (MT+IVT) and without pre-treatment with intravenous thrombolysis (MT-IVT). *Reported data on first pass only. CI indicates confidence interval.

Mistry Stroke 2017

Combined Intravenous Thrombolysis and Thrombectomy vs Thrombectomy Alone for Acute Ischemic StrokeA Pooled Analysis of the SWIFT and STAR Studies

- post hoc analysis used data from 291 patients treated with mechanical thrombectomy included in 2 large multicenter clinical trials;
- 55% received intravenous thombolysis in addition to mechanical thrombectomy, and 45% underwent only mechanical thrombectomy.
- After adjustment for potential confounders, no difference was found between the 2 groups in any of the clinical or radiologic outcomes studied.

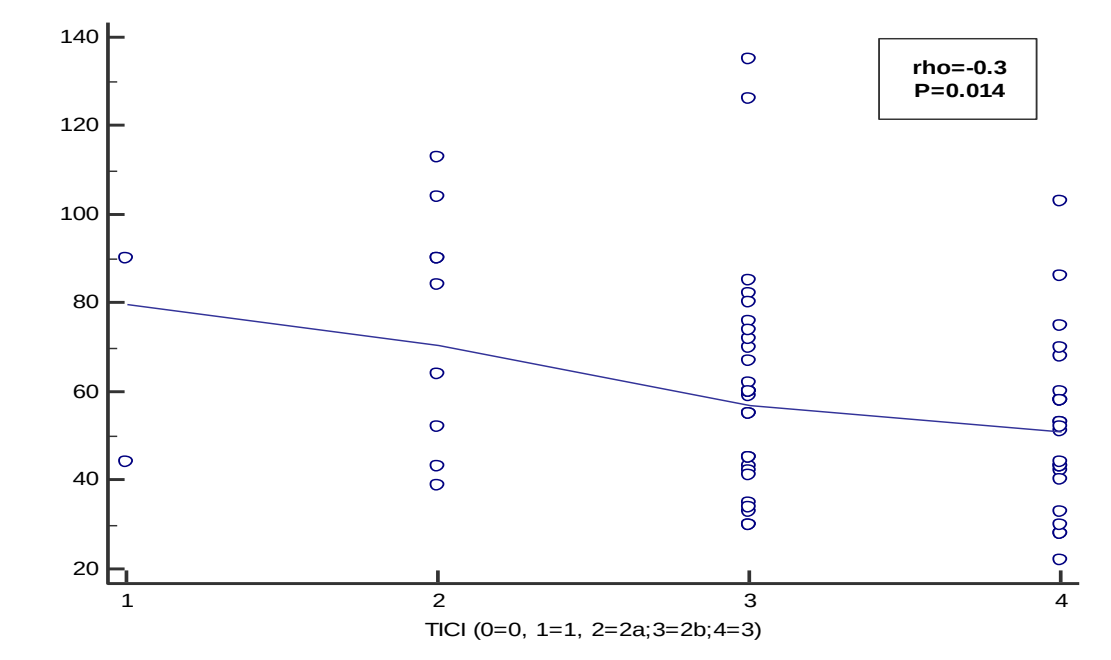
Coutinho, Jama Neurology 2017

IVT TIME DELY PREDICTS RECNALISATION WITH MT RESULTS FOR 63 PATIENTS WITH IV+MT (TICI 2B-3 VERSUS TICI<2B)

Variable	Odds ratio	95% CI	P value
Door to imaging	1,0284	0,9864 to 1,0721	0,1876
Door to needle	0,9340	0,8928 to 0,9771	**0,0030**
Time IV to IA	1,0208	0,9935 to 1,0488	0,1365
NIH pre thrombolysis	1,0259	0,8806 to 1,1953	0,7426

Area under the ROC curve (AUC)	**0,827**

Inverse correlation between time to lysis and recnalasation TICI score



N Nicastro, presented ESO congress 2016

CONCLUSIONS

- IV thrombolysis is the treatment of choice within the 4h30 delay
- Efficacity of the treatment is time dependant → optimal delay: first hour
- Extension of the therapeutic window is possible thanks to MRI (Diffusion/flair): Wake-up stroke/undetermined onset
- Patients with mild neurological deficit may also benefit from IV thrombolysis, benefit is greatest in presence of proximal vascular occlusion

CONCLUSIONS

- Endovascular treatment (mechanical thrombectomy) is part of the standard treatment of patients with acute stroke and proximal vessel occlusion
- Studies have shown a benefit up to 12h (and possible more)
- Endovascular treament obtains the best results when second generation devices are used (stent retrievers) combined to aspiration procedures
- Better outcomes are achieved when perfusion/collaterals imaging contribute to patient's selection

CONCLUSIONS

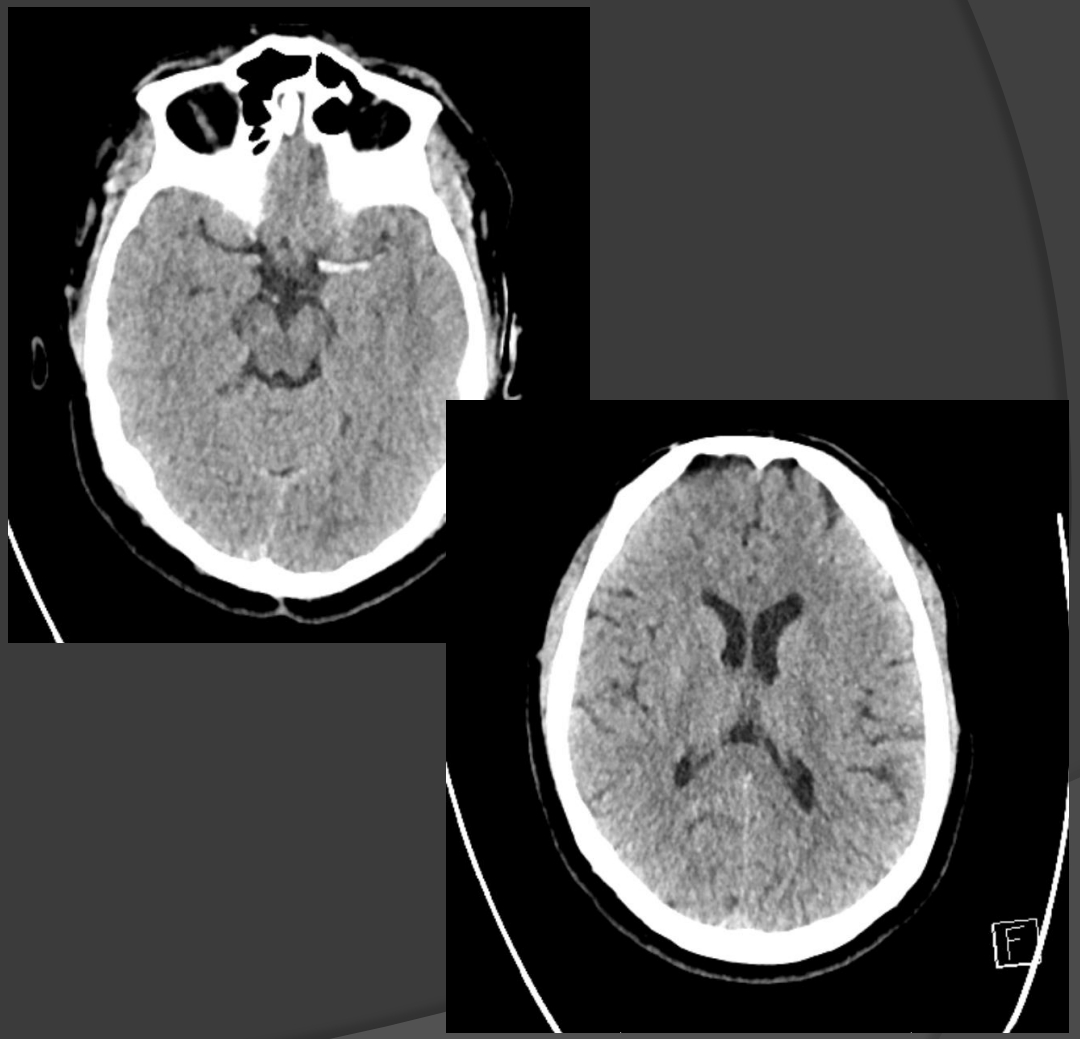
- whether IVT is of added benefit to patients with acute ischemic stroke undergoing mechanical thrombectomy remains still a matter of debate
- prospective studies are needed in order to answer this important issue

thank you for your attention

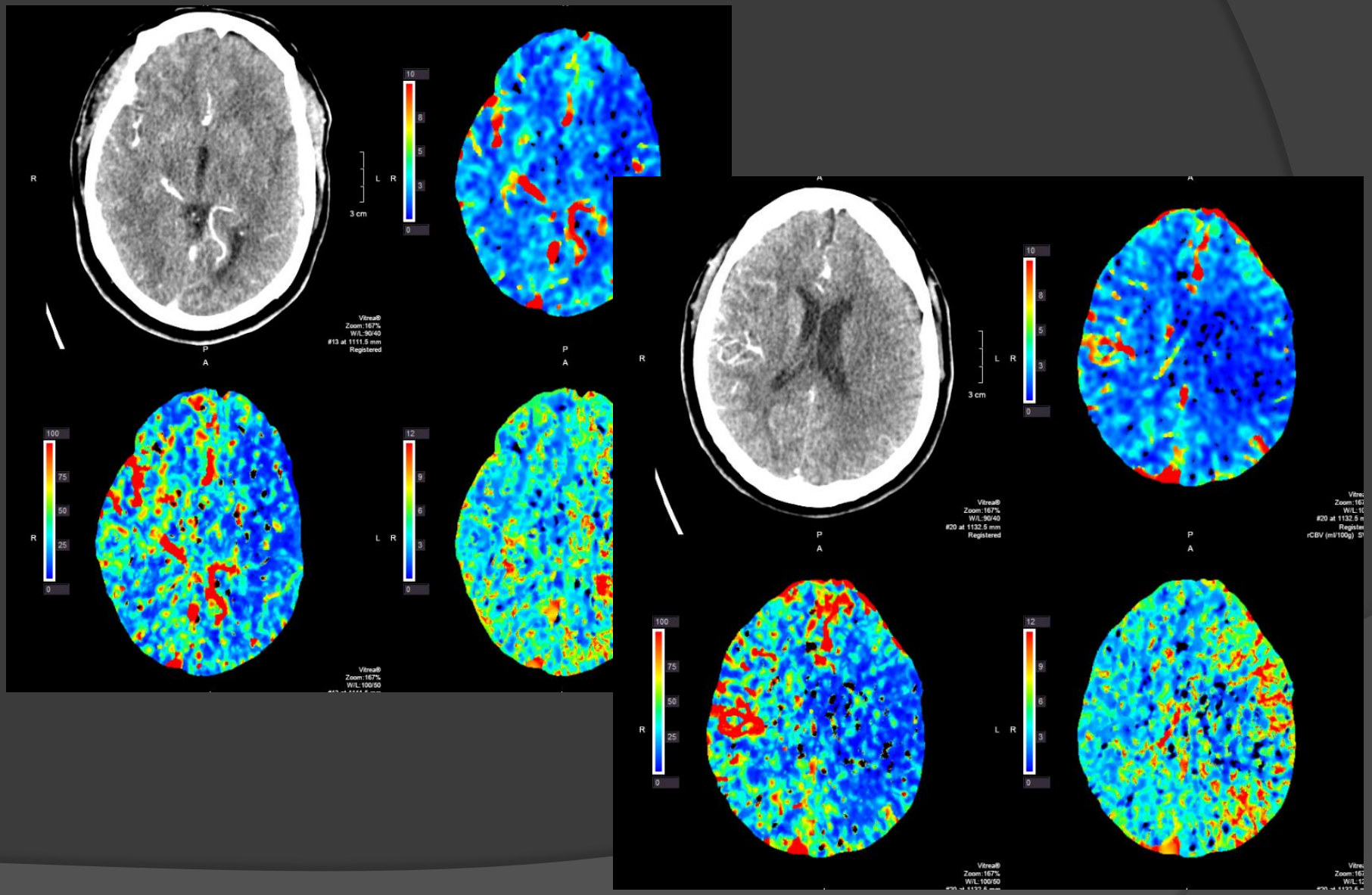
- O.A. Berkhemer, P.S. Fransen, D. Beumer, *et al.***A randomized trial of intraarterial treatment for acute ischemic stroke** New England Journal of Medicine, 372 (2015), pp. 11-20
- M. Goyal, A.M. Demchuk, B.K. Menon, *et al.***Randomized assessment of rapid endovascular treatment of ischemic stroken** New England Journal of Medicine, 372 (2015), pp. 1019-1030
- L. Saver, M. Goyal, A. Bonafe, *et al.***Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke** New England Journal of Medicine, 372 (2015), pp. 2285-2295
- C. Campbell, P.J. Mitchell, T.J. Kleinig, *et al.***Endovascular therapy for ischemic stroke with perfusion-imaging selection** New England Journal of Medicine, 372 (2015), pp. 1009-1018
- G. Jovin, A. Chamorro, E. Cobo, *et al.***Thrombectomy within 8 hours after symptom onset in ischemic stroke** New England Journal of Medicine, 372 (2015), pp. 2296-2306

56 years old patient known for ischemic cardiopathy anf AF, presents aphasia and right hemisyndrom

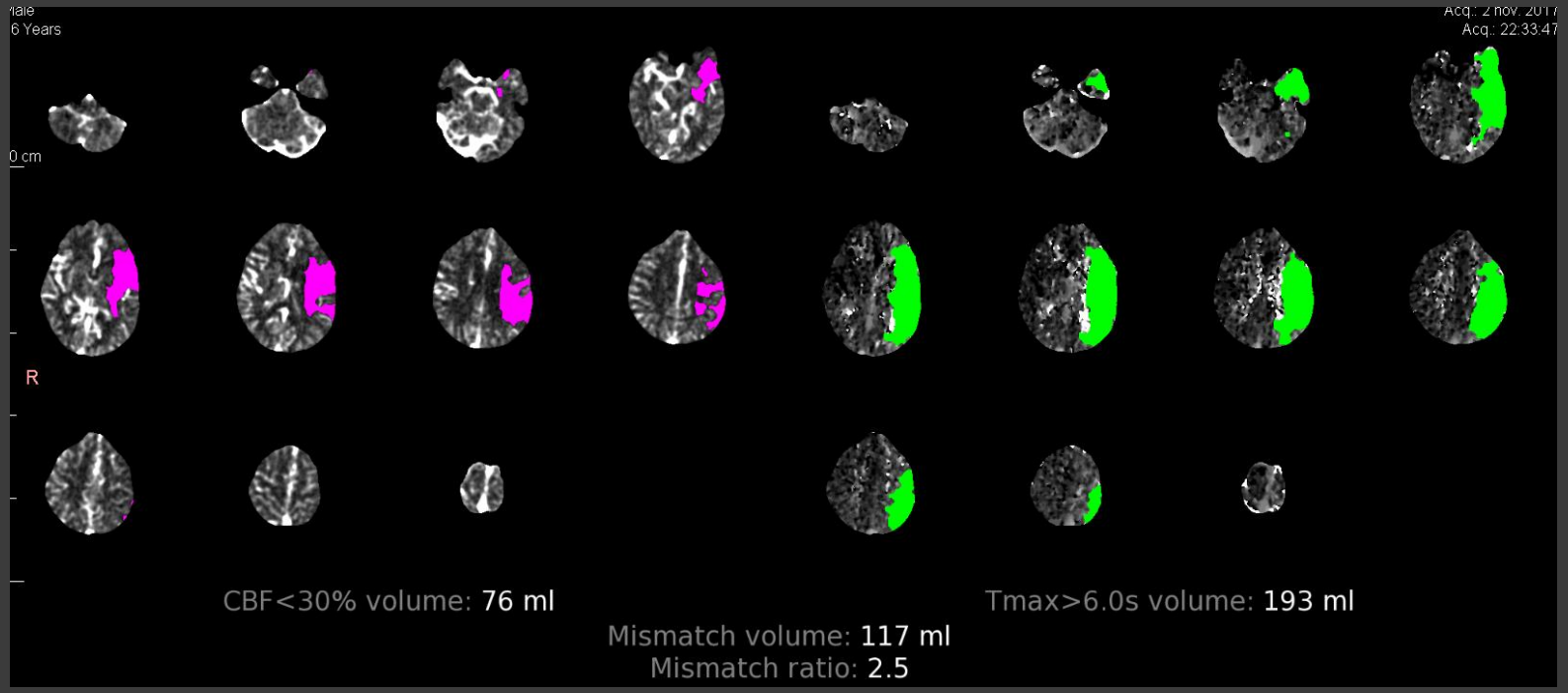
- **Admission 115 min after stroke onset**
- **NIHSS is 29**



Perfusion CT maps



PERFUSION CT MAPS (RAPID)



CT-scan after 24 hours NIHSS 24

SUBGROUP ANALYSIS

Bush CK, Plos one, 2016

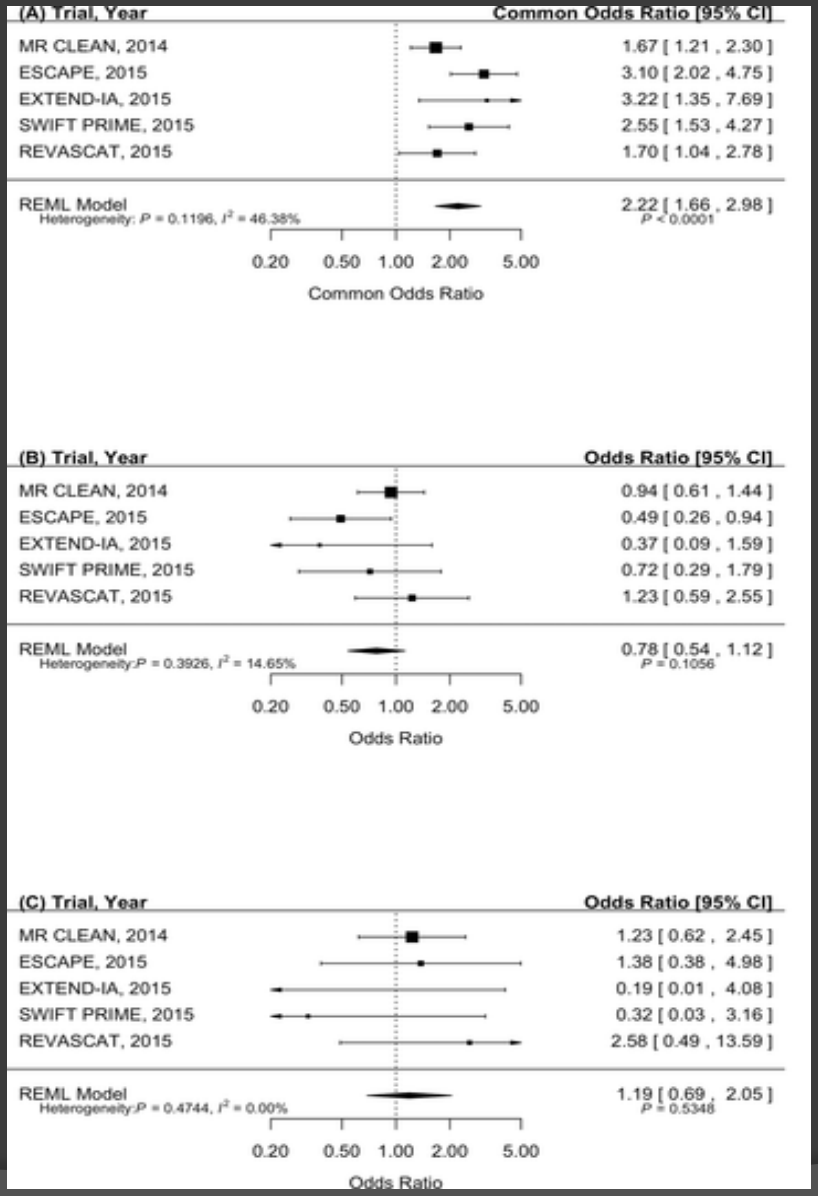
	Ordinal Analysis of mRS Scores at 90 Days			
	Number of Studies	Pooled OR [95% CI]	Effect P	Subgroup P[a]
Overall Analysis	5	2.22 [1.66, 2.98]	<0.0001	
Gender				
M				0.9255
Fe				
Ag				
<				0.8783
≥ 70 years	4 [13–14, 16–17]	2.26 [1.20, 4.26]	0.0113	
NIHSS Score				
< 17	3 [13, 16–17]	1.77 [1.22, 2.58]	0.0028	0.3761
≥ 17	4 [13–14, 16–17]	2.23 [1.58, 3.15]	<0.0001	
ASPECTS Score				
Low (< 8)	4 [13–14, 16–17]	1.82 [1.19, 2.79]	0.0061	0.5274
High (≥ 8)	4 [13–14, 16–17]	2.19 [1.61, 2.98]	<0.0001	
IV Alteplase				
Given	3 [13–14, 17]	1.85 [1.39, 2.46]	<0.0001	0.1884
Not Given	5 [13–17]	2.41 [1.76, 3.31]	<0.0001	

[a] P-values for subgroup differences, i.e. omnibus test of moderator coefficients from mixed-effects meta-regression models. Abbreviations: mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early Computed Tomography Score [25, 26]; IV, intravenous.

doi:10.1371/journal.pone.0147287.t004

No siginificant difference regarding benefit of endovascular treatment and different subgroups

PROGNOSIS



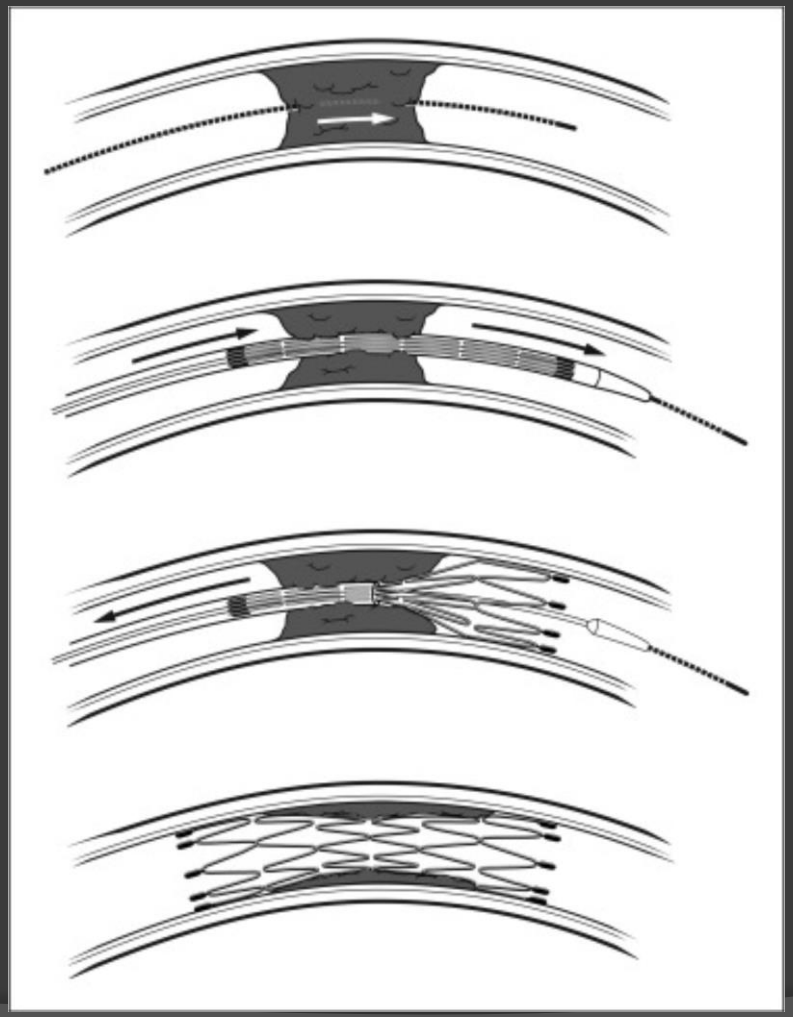
A. 3 months functional prognosis
médical (OR 2.2 95%CI,1.66to 2.98;P<0.0001).

B. Mortality
OR 0.78, IC 95% 0.54,1.12, p =0.1056 o

C. IC hemorrhage
OR 1.19 IC 95%, 0.69-2.05 p= 0.5348

Bush CK, Plos one, 2016

Deployment of expandable stent for the revascularization of large vessels



Wingspan (Stryker Neurovascular, Fremont, CA)
Neuroform (Stryker Neurovascular)
Enterprise (Codman, Raynham, MA)
Solitaire
Trevo

Potential limitations of use of stent retrievers

- Solitaire and Trevo devices may cause vascular damage that extends into the medial layer (animal studies) The clinical significance of this finding remains to be investigated
- stent retriever may induce clot fragmentation, which may result in distal embolization and occlusion of previously uninvolved territory

Journal of NeuroInterventional Surgery, 2015

The Use and Utility of Aspiration Thrombectomy in Acute Ischemic Stroke: A Systematic Review and Meta-Analysis

- 5 studies investigated aspiration thrombectomy only, and 16 studies investigated a Direct Aspiration First Pass Technique for acute ischemic stroke (ADAPT)
- of the 16 studies on ADAPT, the rate of successful recanalization (TICI 2b/3) was 89.3%
- proportion of patients with good clinical outcome (90-day mRS ≤2) was 52.7%

Wei D, AJNR 2017

A DIRECT ASPIRATION FIRST-PASS TECHNIQUE VS STENTRIEVER THROMBECTOMY IN EMERGENT LARGE VESSEL INTRACRANIAL OCCLUSIONS

- 117 patients were included
- Direct Aspiration First Pass Technique for acute ischemic stroke (ADAPT) was used in 47 patients, 20 (42.5%) required rescue stent retriever thrombectomy and primary stent retriever thrombectomy was performed in 70 patients:
  - Procedural time (54.0 vs 77.1 minutes; $p < 0.01$)
  - time to a TICI score (294.3 vs 346.7 minutes; $p < 0.01$) was lower in the ADAPT group
  - TICI 2b/3 recanalization rates were similar between the ADAPT and stent retriever groups (82.9% vs 71.4%; $p = 0.19$).
  - good functional outcome (mRS 0-2) at 90 days were similar between the ADAPT and stent retriever groups (48.9% vs 41.4%; $p = 0.45$)

Stapleton, J Neurosurg 2017

The Use and Utility of Aspiration Thrombectomy in Acute Ischemic Stroke: A Systematic Review and Meta-Analysis

- The newer generation of the Penumbra aspiration system:
  - revascularization rate of 91% with the new Penumbra device compared to 82% in the initial Penumbra pivotal trial
  - revascularization is achieved within a mean time of 20 min, compared to 45 min in the initial trial

Intravenous Thrombolysis Facilitates Successful Recanalization with Stent-Retriever Mechanical Thrombectomy in Middle Cerebral Artery Occlusions

Table 3. Analysis of all MCA occlusions (N = 93): comparison of patients with successful recanalization (mTICI 2b and 3) versus patients without successful recanalization (mTICI 0-2a)

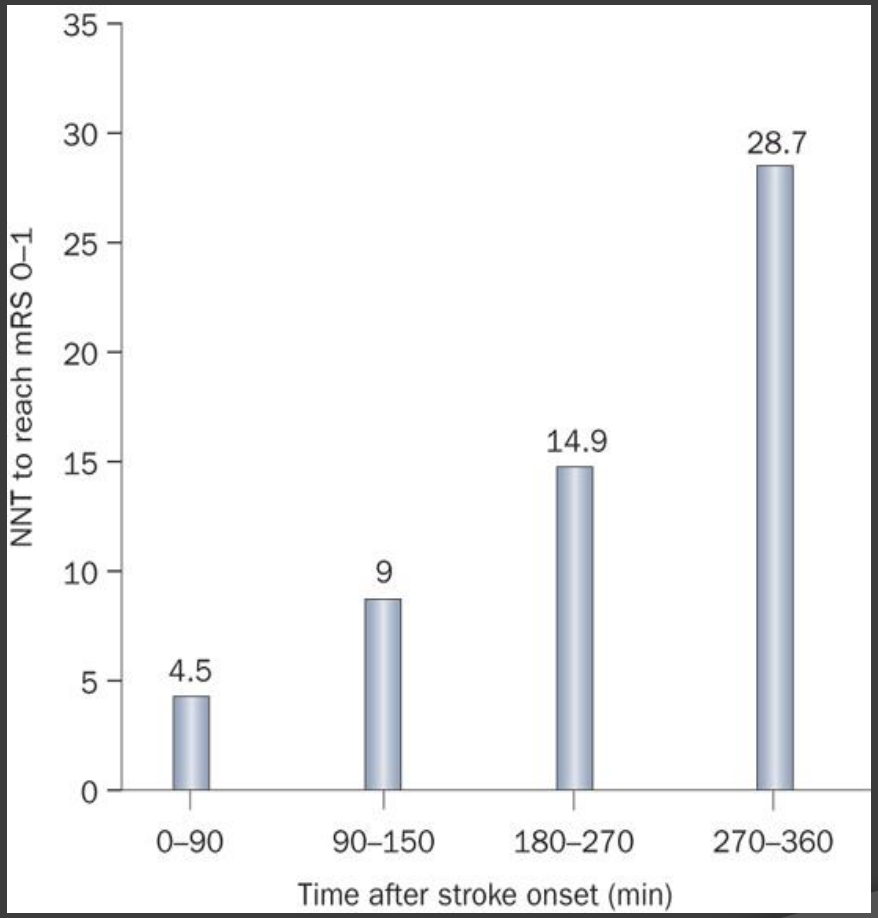
Characteristics	mTICI 2b and 3 (n = 77)	mTICI 0-2a (n = 16)	*P* value
MCA M2, n (%)	10 of 77 (13%)	3 of 16 (19)	.70
Age (years), median (range)	74 (32-94)	74 (65-91)	.08
Baseline NIHSS score, mean (±SD)	16 (±6)	18 (±8)	.80
Thrombus length (mm), median (range)	10 (3-26)	19 (6-23)	.003
Thrombus length (≤15 mm), n (%)	60 of 75 (80)*	4 of 15 (27)*	.0001
Atrial fibrillation, n (%)	42 of 77 (55)	11 of 16 (69)	.40
No of stent retriever passes (≤2), n (%)	50 of 77 (65)	2 of 16 (13)	.0002
Concomitant IVT, n (%)	59 of 77 (77)	7 of 16 (44)	.01
Time from symptom onset to groin puncture (min), median (range)	190 (72-396)	197 (163-343)	.10
Time from groin puncture to final recanalization (min), median (range)	44 (10-117)	73 (45-203)	<.0001
Time from groin puncture to final recanalization (≤1 h), n (%)	51 of 77 (66)	3 of 16 (19)	.0006

Abbreviations: IVT, intravenous thrombolysis; MCA, middle cerebral artery; mTICI, modified Treatment in Cerebral Ischemia; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation.

*

Behme, J of Stroke and Cerebrovasc Dis 2016

Number of patients needed to treat in order to avoid infavourable prognosis



Donnan, G. A. et al. Nat. Rev. Neurol. 2011