Triage of patients for thrombectomy

ECMINT 3.3, Oxford, 16th-20th December 2019

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University Institute of Diagnostic and Interventional Neuroradiology
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Director and Chair: Prof. J. Gralla

Randomized controlled trials: Stent retriever thrombectomy and medical management versus medical management alone

2014 / 2015

MR CLEAN

ESCAPE

EXTEND-IA

SWIFT PRIME

REVASCAT

Endovascular stent retriever thrombectomy:

The new standard of care for large vessel ischemic stroke!

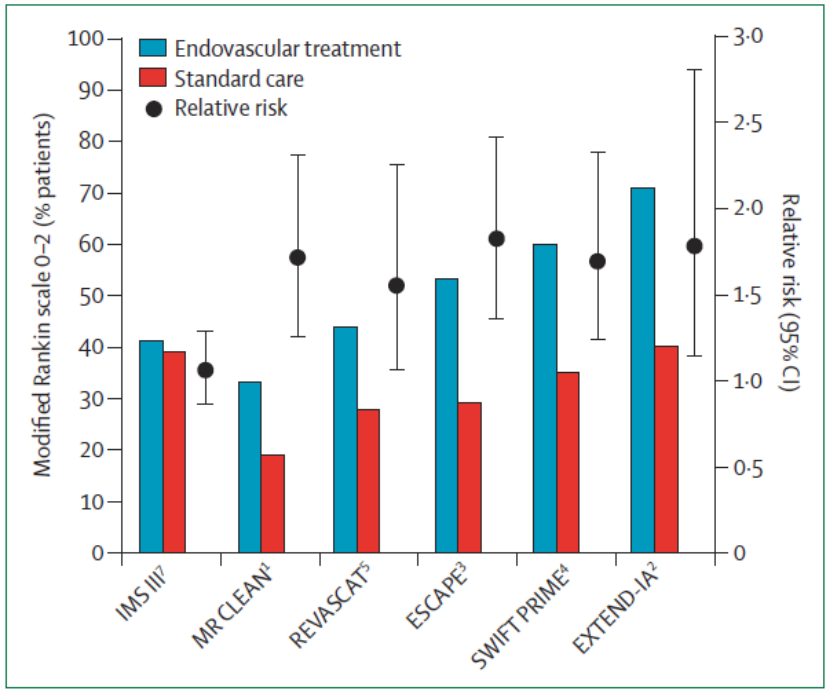

Figure 1: Functional outcome of patients with ischaemic stroke in trials of endovascular thrombectomy

Acute ischemic stroke

1. Stroke is an emergency –
Decisions are made in an emergency setting

2. EVT is effective: Recanalization!

3. The next stroke coming to your hospital will be an individual patient – not a cohort

Natural history of LVO acute ischemic stroke

	Poor outcome (mRS 3-5)	Mortality
M1 occlusion	87%	12%
Carotid-T occlusion	92%	23%
Tandem occlusion	90%	30%
BA occlusion	65% (mRS 4-5)	40%
M2 occlusion	47%	3%

Hernandez-Perez et al. J Neurimaging 2014; Nanduri et al. Stroke 2018; Schonewille et al. JNNP 2005

Outcome: 3 months mRS

- Any reasonable chance of a shift between mRS 0 and 5 is appreciated and clinically valuable
- Patients with a low potential to achieve mRS 0-2 should not be considered as candidates for futile recanalization per se

Meta-analysis RCT

HERMES Collaborators

Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials

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

Mayank Goyal, Bijoy K Menon, Wim H van Zwam, Diederik W J Dippel, Peter J Mitchell, Andrew M Demchuk, Antoni Dávalos, Charles B L M Majoie, Aad van der Lugt, Maria A de Miquel, Geoffrey A Donnan, Yvo B W E M Roos, Alain Bonafe, Reza Jahan, Hans-Christoph Diener, Lucie A van den Berg, Elad I Levy, Olvert A Berkhemer, Vitor M Pereira, Jeremy Rempel, Mònica Millán, Stephen M Davis, Daniel Roy, John Thornton, Luis San Román, Marc Ribó, Debbie Beumer, Bruce Stouch, Scott Brown, Bruce C V Campbell, Robert J van Oostenbrugge, Jeffrey L Saver, Michael D Hill, Tudor G Jovin, for the HERMES collaborators

MR CLEAN

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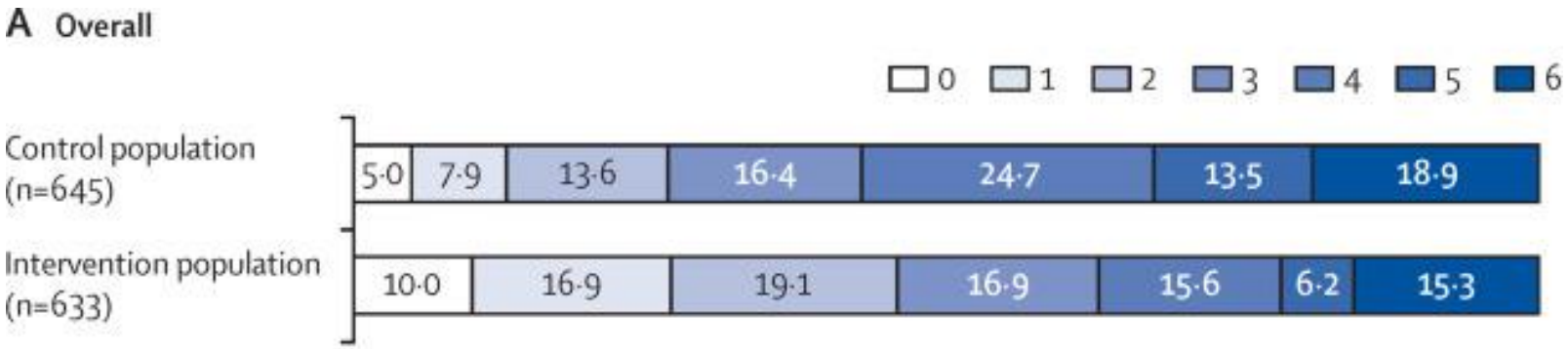
- **Pooled patient-level data**
- **1287 patients**

Lancet 2016; 387: 1723–31

Meta-analysis RCT
Overall treatment effect

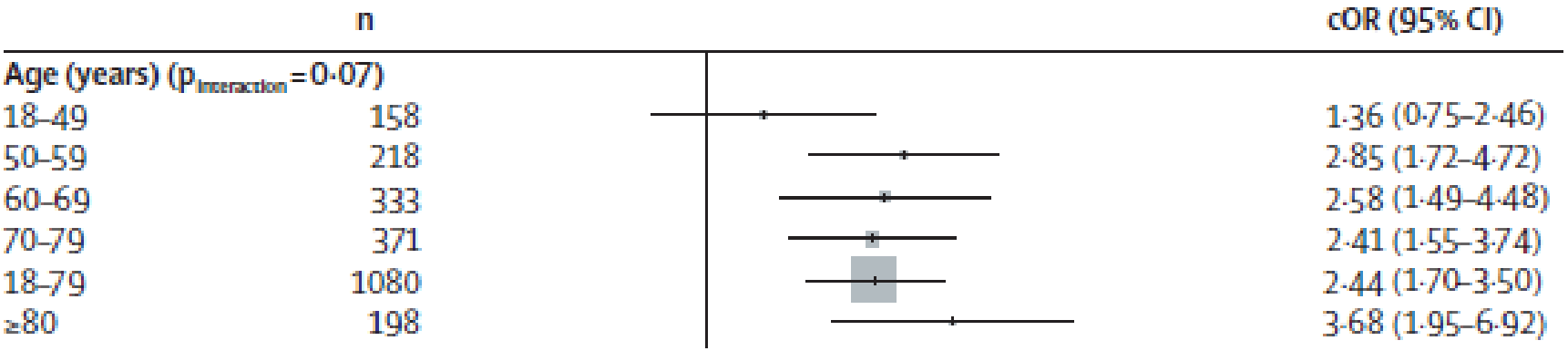
NNT 2.6



The number needed to treat with endovascular thrombectomy to reduce disability by at least one level on mRS for one patient was **2.6.**

Goyal et al. Lancet 2016

Meta-analysis RCT
Age



- All age groups benefit
- Elderly patients (octogenerians) benefit as well

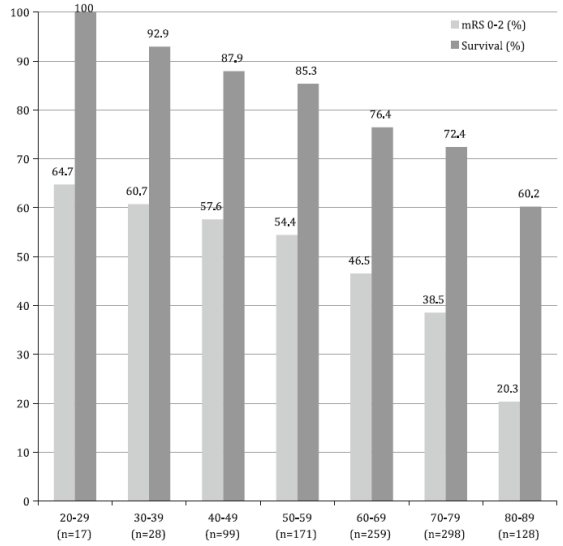
Goyal et al. Lancet 2016

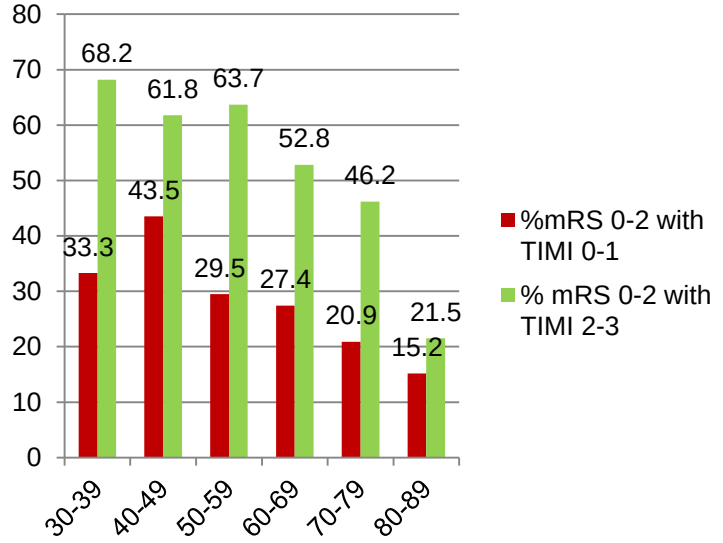
Age

Age dependency of safety and outcome of endovascular therapy for acute stroke

Rudolf Luedi · Kety Hsieh · Agnieszka Slezak · Marwan El-Koussy · Urs Fischer · Mirjam R. Heldner · Julia Meisterernst · Marie-Luise Mono · Christoph Zubler · Pasquale Mordasini · Christoph Ozdoba · Heinrich P. Mattle · Gerhard Schroth · Jan Gralla · Marcel Arnold · Simon Jung

Fig. 1 Percentage of favorable outcome (mRS 0–2) and survival after 3 months for each life decade of 1,000 patients after endovascular treatment

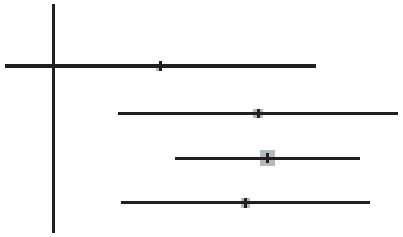




- Linear relationship between age and outcome
  ➡ ever increase in 26 years of age was associated with an increase in mRS of 1 point
- Age no risk factor for sICH or lower racanalization success

Meta-analysis RCT
NIHSS

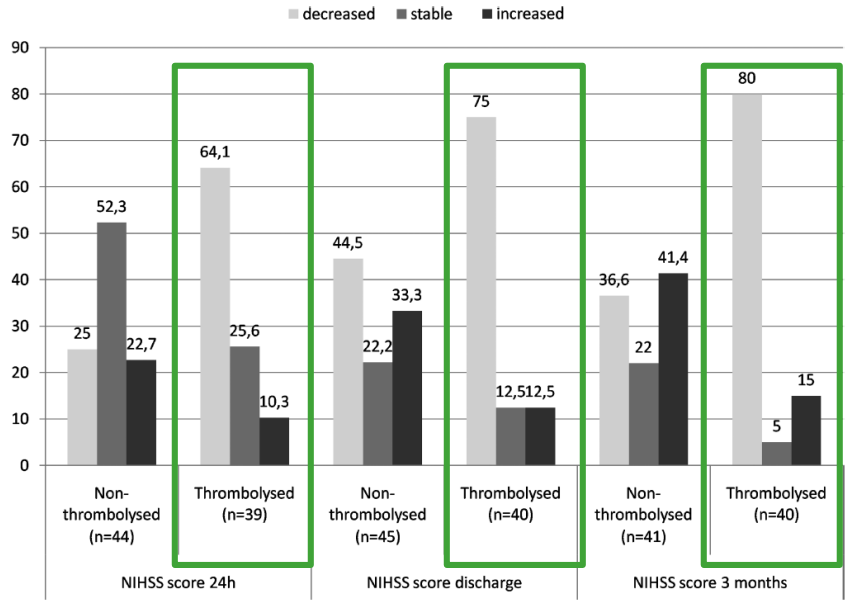
NIHSS score ($p_{interaction}$ = 0·45)		
≤10	177	1·67 (0·80–3·50)
11–15	307	2·68 (1·39–5·19)
16–20	473	2·81 (1·80–4·38)
≥21	321	2·52 (1·40–4·54)



- Consistent treatment effect over all stroke severity categories
- Uncertainty about very mild symptoms (NIHSS 1-5)

Outcome of patients with occlusions of the internal carotid artery or the main stem of the middle cerebral artery with NIHSS score of less than 5: comparison between thrombolysed and non-thrombolysed patients

Mirjam R Heldner,[1] Simon Jung,[1,2] Christoph Zubler,[2] Pasquale Mordasini,[2] Anja Weck,[1] Marie-Luise Mono,[1] Christoph Ozdoba,[2] Marwan El-Koussy,[2] Heinrich P Mattle,[1] Gerhard Schroth,[2] Jan Gralla,[2] Marcel Arnold,[1] Urs Fischer[1]



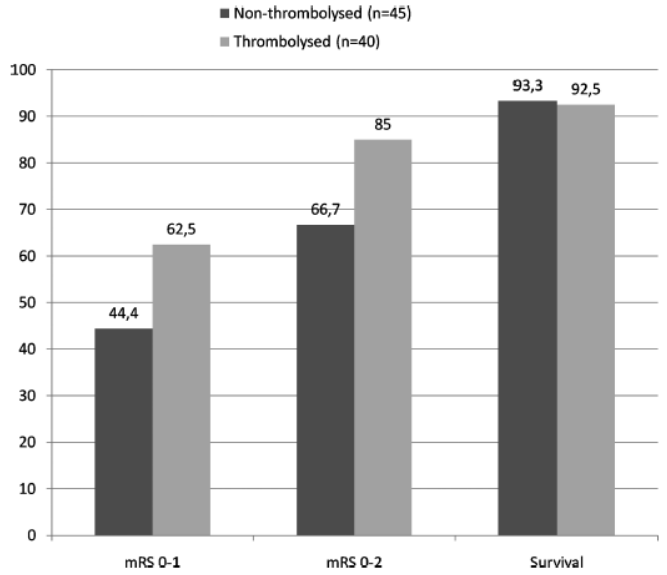
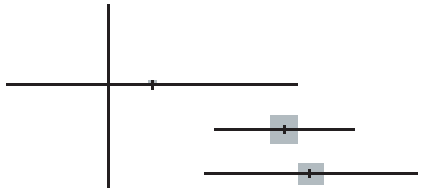


Figure 2 Percentage of survival and excellent/favourable outcomes at 3 months.

- Non-thrombolysed patients with mild deficits and large vessel occlusion deteriorated significantly more often within 3 months then thrombolysed patients

Meta-analysis RCT
ASPECTS

ASPECTS ($p_{interaction}$ = 0·29)		
0–5	121	1·24 (0·62–2·49)
6–8	475	2·34 (1·68–3·26)
9–10	682	2·66 (1·61–4·40)

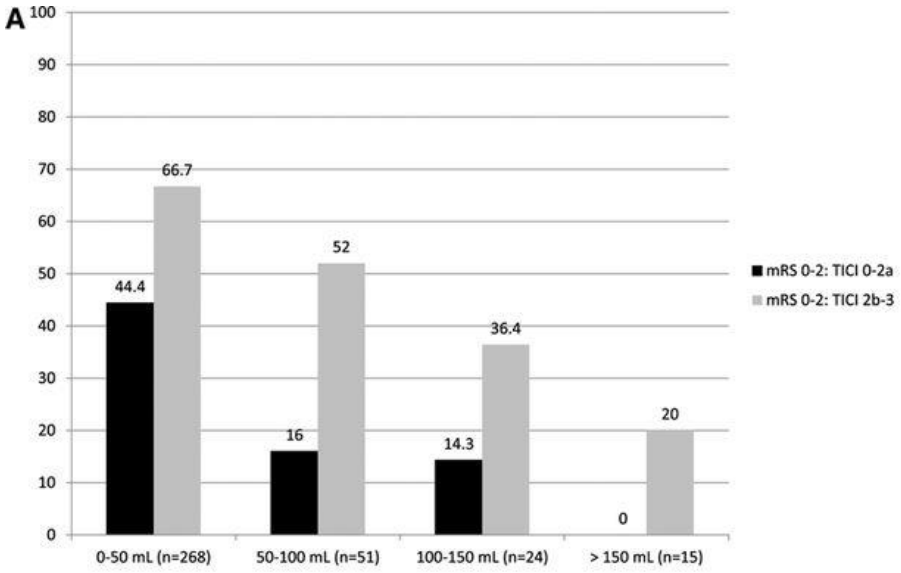


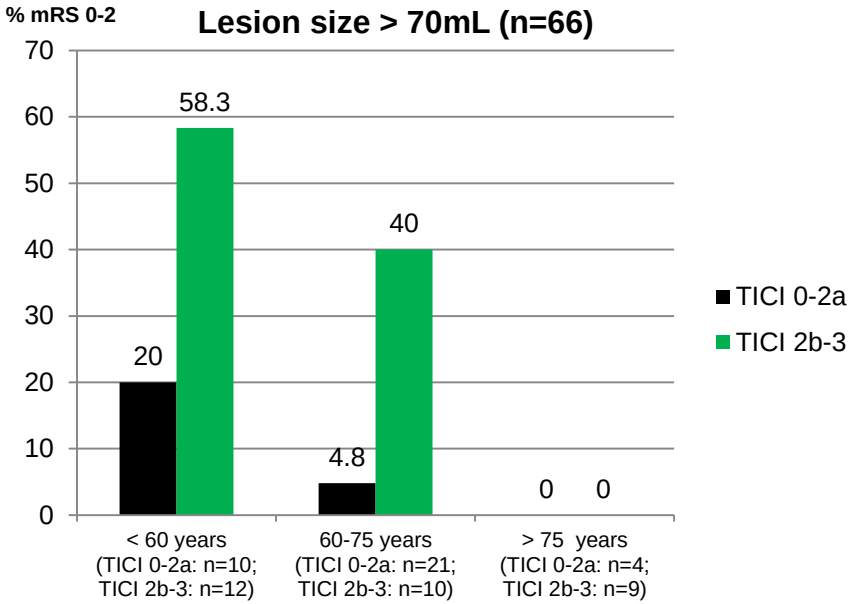
- Treatment effect is present for all ASPECTS categories
- More data needed for large infarcts (ASPECTS 0-5)

Goyal et al. Lancet 2016

Younger Stroke Patients With Large Pretreatment Diffusion-Weighted Imaging Lesions May Benefit From Endovascular Treatment

Marc D. Gilgen, MSc*; Dariusz Klimek*; Kai T. Liesirova, MD; Julia Meisterernst; Pascal P. Klinger-Gratz, MD; Gerhard Schroth, MD; Pasquale Mordasini, MD; Kety Hsieh, MD; Johannes Slotboom, PhD; Mirjam R. Heldner, MD; Anne Broeg-Morvay; Marie-Luise Mono, MD; Urs Fischer, MD; Heinrich P. Mattle, MD; Marcel Arnold, MD; Jan Gralla, MD; Marwan El-Koussy, MD*; Simon Jung, MD*



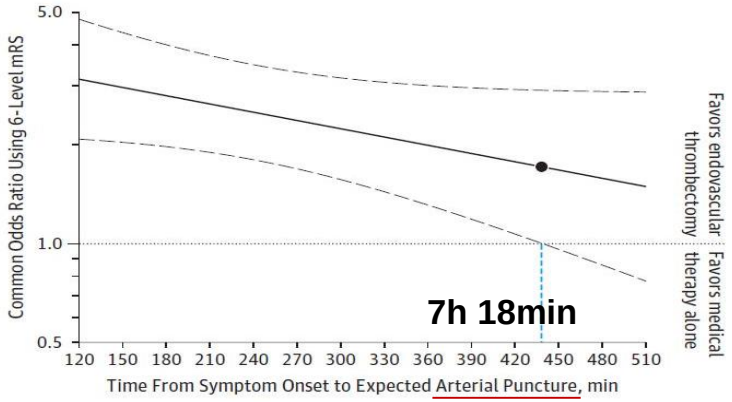


- Every third patient with lesion > 100 mL reached favourable outcome in case of good reperfusion.
- We cannot identify a reasonable cut-off value of lesion volume.
- Therapy may be considered in patients with large DWI lesions, especially if they are younger.
- Future trials should include these patients.

RCTs for thrombectomy beyond 6 hour time window 2018

Thrombectomy beyond 6h time window

Clinical outcomes does **not only depend on time of reperfuison**, but on a **function of tissue perfusion** sustained by **collateral flow** and **regional susceptibility to early ischemic changes**



Outcomes = Collaterals / Time

[1] Saver et al. JAMA 2016; [2] Powers et al. Stroke 2015; [3] Wahlgren et al. Int J Stroke 2016; [4] Jovin et.al. Stroke 2011

Thrombectomy beyond 6h time window

DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 4, 2018 VOL. 378 NO. 1

Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct

R.G. Nogueira, A.P. Jadhav, D.C. Haussen, A. Bonafe, R.F. Budzik, P. Bhuva, D.R. Yavagal, M. Ribo, C. Cognard, R.A. Hanel, C.A. Sila, A.E. Hassan, M. Millan, E.I. Levy, P. Mitchell, M. Chen, J.D. English, Q.A. Shah, F.L. Silver, V.M. Pereira, B.P. Mehta, B.W. Baxter, M.G. Abraham, P. Cardona, E. Veznedaroglu, F.R. Hellinger, L. Feng, J.F. Kirmani, D.K. Lopes, B.T. Jankowitz, M.R. Frankel, V. Costalat, N.A. Vora, A.J. Yoo, A.M. Malik, A.J. Furlan, M. Rubiera, A. Aghaebrahim, J.-M. Olivot, W.G. Tekle, R. Shields, T. Graves, R.J. Lewis, W.S. Smith, D.S. Liebeskind, J.L. Saver, and T.G. Jovin, for the DAWN Trial Investigators*

defuse·3

Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3 Trial

ORIGINAL ARTICLE

Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging

G.W. Albers, M.P. Marks, S. Kemp, S. Christensen, J.P. Tsai, S. Ortega-Gutierrez, R.A. McTaggart, M.T. Torbey, M. Kim-Tenser, T. Leslie-Mazwi, A. Sarraj, S.E. Kasner, S.A. Ansari, S.D. Yeatts, S. Hamilton, M. Mlynash, J.J. Heit, G. Zaharchuk, S. Kim, J. Carrozzella, Y.Y. Palesch, A.M. Demchuk, R. Bammer, P.W. Lavori, J.P. Broderick, and M.G. Lansberg, for the DEFUSE 3 Investigators*

Thrombectomy beyond 6h time window

DWI or CTP - clinical mismatch

- Last been known to be well 6-24 hrs
- **Clinical imaging/core mismatch (CIM):** mismatch between severity of clinical deficit and infarct volume, signifying substantial tissue at risk

A. Age ≥ 80 years old:
   1. NIHSS ≥ 10 + core infarct <21 cc
B. Age < 80 years old:
   2. NIHSS ≥ 10 + core infarct <31 cc
   3. NIHSS ≥ 20 + core infarct <51 cc

DWI or CTP – imaging mismatch

- Last been known to be well 6-16 hrs
- **Imaging perfusion/core mismatch:** target mismatch between infarct core and volume of ischemic tissue based on ***imaging criteria***

- Infarct core <70 ml
- Mismatch ratio ≥1.8
- Mismatch volume ≥ 15 ml (Tmax <6 sec)
- NIHSS ≥ 6

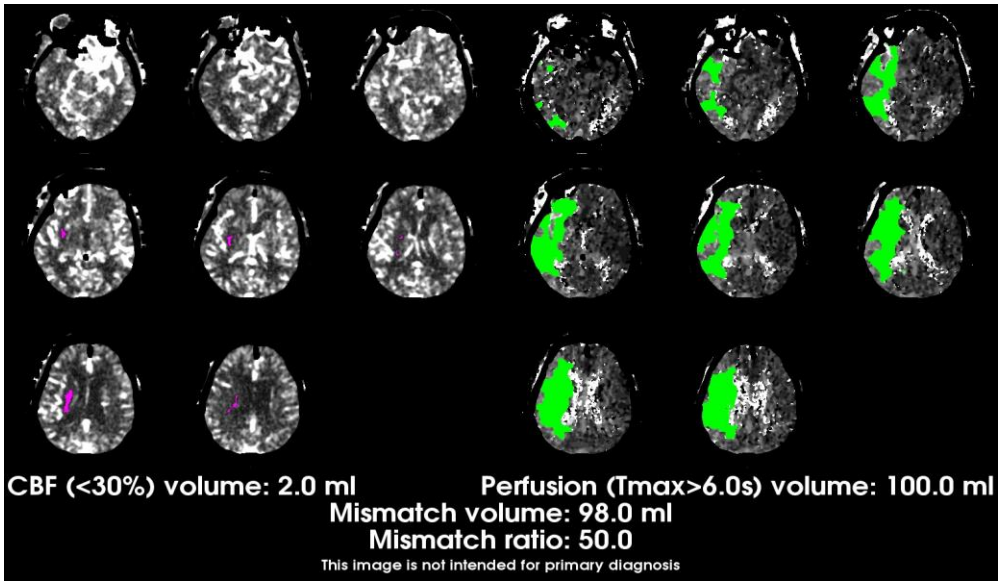
Imaging inclusion criteria

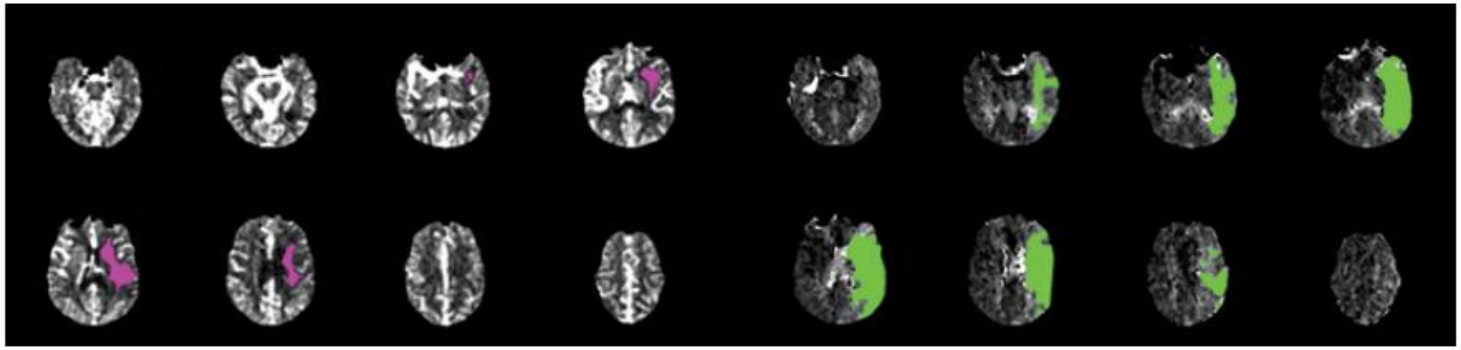
Rapid® software iSchemaView

Core:
- DWI ADC <620x10^{-3} mm/s
- CBF <30%

Penumbra: Tmax >6 sec

➡ Single parameter, single threshold-based (linear models)!



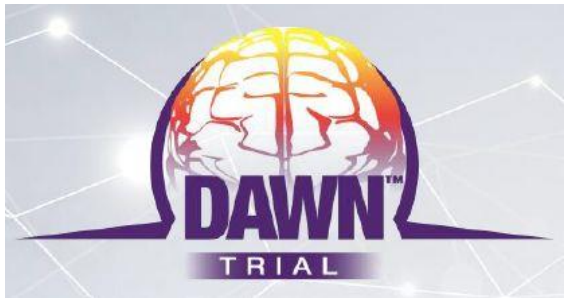


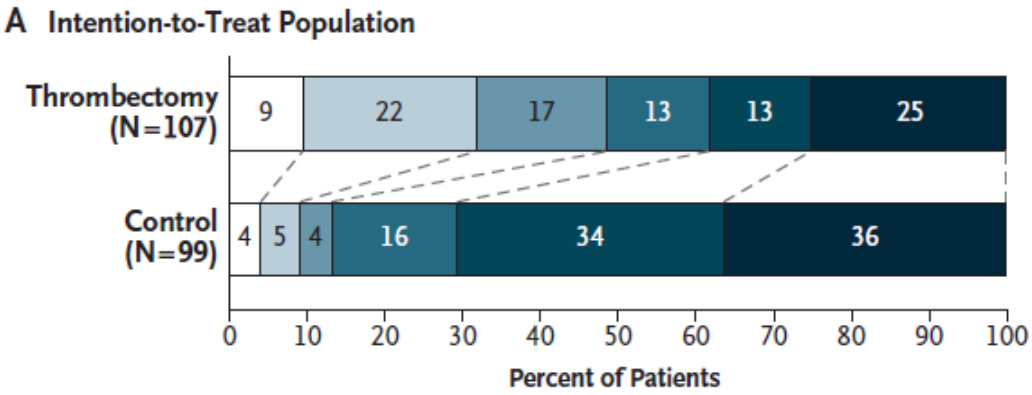
Volume of Ischemic Core, 23 ml

Volume of Perfusion Lesion, 128 ml

Mismatch volume, 105 ml
Mismatch ratio, 5.6

Thrombectomy beyond 6h time window





Δ 36%

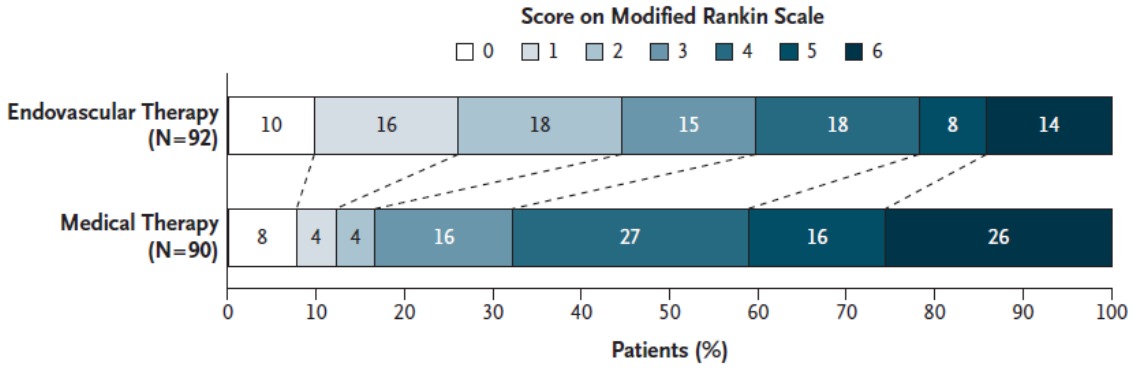
	MT	Control	Treatment benefit (95% CI)	Bayesian probability of superiority
Day 90 weighted mRS	5.5 ± 3.8	3.4 ± 3.1	2.1 (1.2-3.1)	>0.9999*
Day 90 mRS (0-2)	49%	13%	36% (24%-47%)	>0.9999*

***Similar to p<0.0001**

NNT for 90-day functional independence = 2.8

Thrombectomy beyond 6h time window

defuse 3

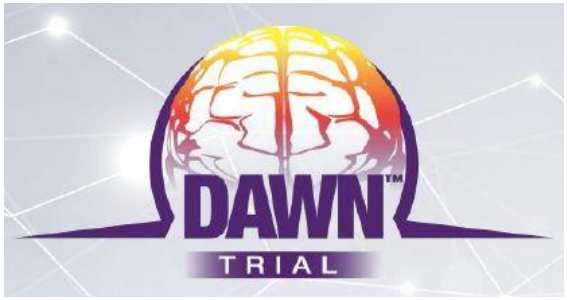


Δ 28%

	MT	Control	(c)OR (95% CI)	P Value
Day 90 median mRS	3 (1 – 4)	4 (3 – 6)	2.77 (1.63 - 4.70)	<0.001
Day 90 mRS (0-2)	45%	17%	2.67 (1.60 – 4.48)	<0.001

NNT for 90-day functional independence = 2

Thrombectomy beyond 6h time window



defuse·3

	Recanalization and Safety outcomes	
	DAWN	DEFUSE 3
TICI 2B/3	84%	76%
sICH		
EVT	6%	7%
Control	3%	4%
Mortality		
EVT	25%	14%
Control	36%	26%

AHA/ASA Stroke Guidelines 2018

AHA/ASA Guideline

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

Reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

Endorsed by the Society for Academic Emergency Medicine and Neurocritical Care Society

The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.

William J. Powers, MD, FAHA, Chair; Alejandro A. Rabinstein, MD, FAHA, Vice Chair; Teri Ackerson, BSN, RN; Opeolu M. Adeoye, MD, MS, FAHA; Nicholas C. Bambakidis, MD, FAHA; Kyra Becker, MD, FAHA; José Biller, MD, FAHA; Michael Brown, MD, MSc; Bart M. Demaerschalk, MD, MSc, FAHA; Brian Hoh, MD, FAHA; Edward C. Jauch, MD, MS, FAHA; Chelsea S. Kidwell, MD, FAHA; Thabele M. Leslie-Mazwi, MD; Bruce Ovbiagele, MD, MSc, MAS, MBA, FAHA; Phillip A. Scott, MD, MBA, FAHA; Kevin N. Sheth, MD, FAHA; Andrew M. Southerland, MD, MSc; Deborah V. Summers, MSN, RN, FAHA; David L. Tirschwell, MD, MSc, FAHA; on behalf of the American Heart Association Stroke Council

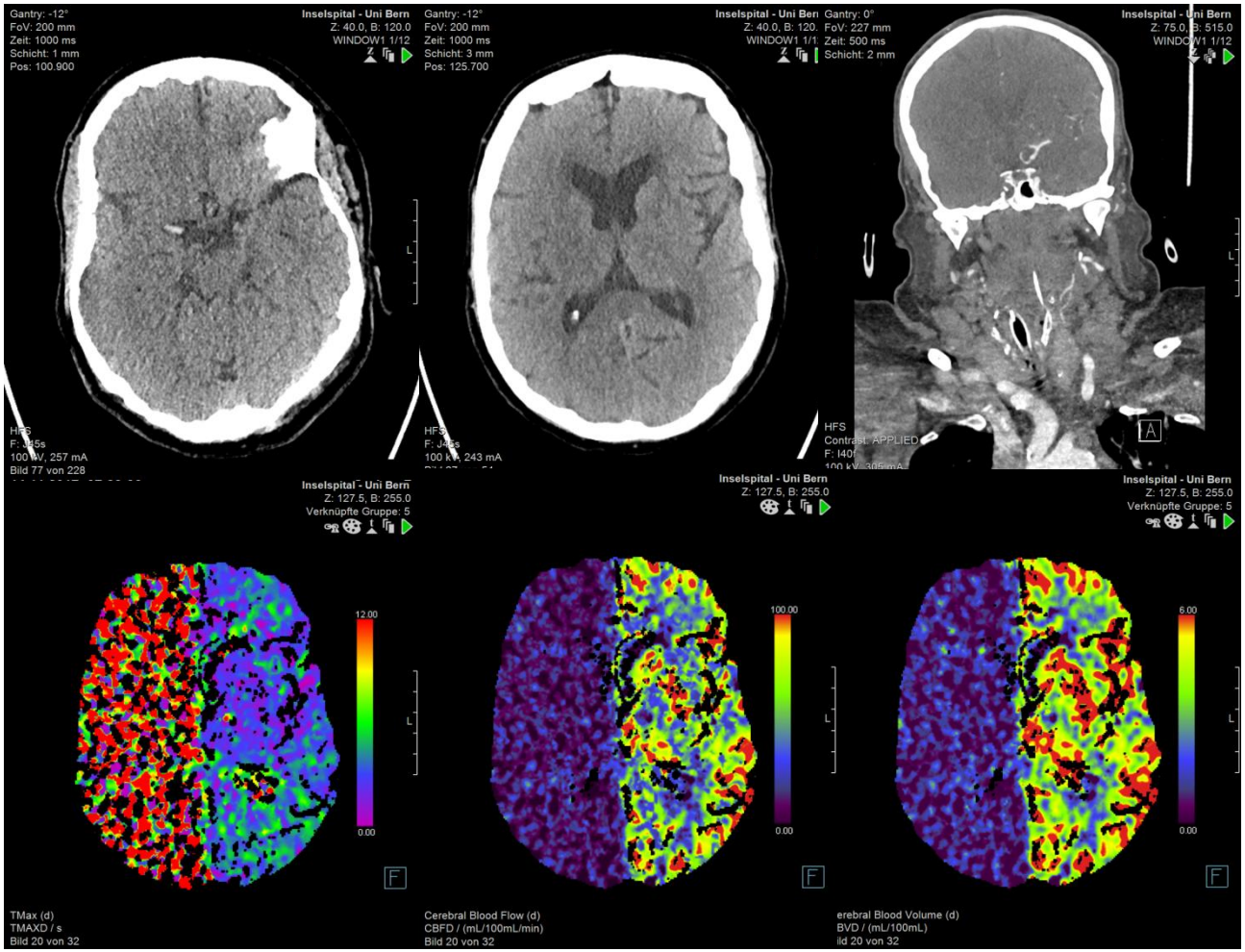
Decision making

Refuse treatment - based on what?

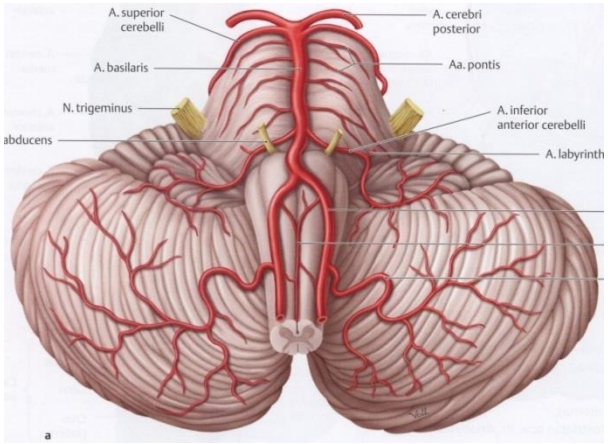
Age ?
NIHSS ?
ASPECTS score ?
Late time window ?
Mismatch?
DWI-infarct volume?
Clinical prognosis scales?
Cost-effectiveness?

Who not to treat?

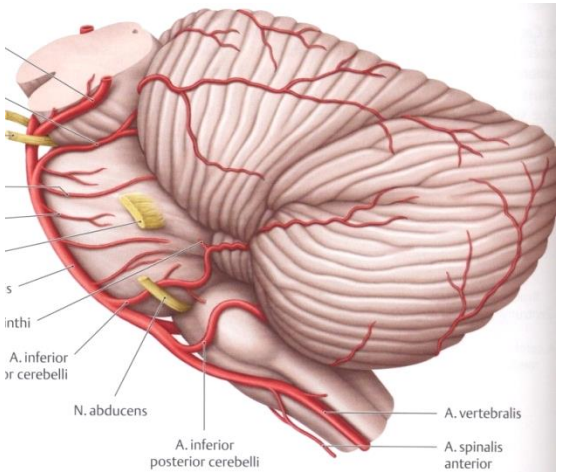
- 58-year old female, wake-up stroke, found at 4 am, hemiplegic, NIHSS > 20, GCS 7, intubated

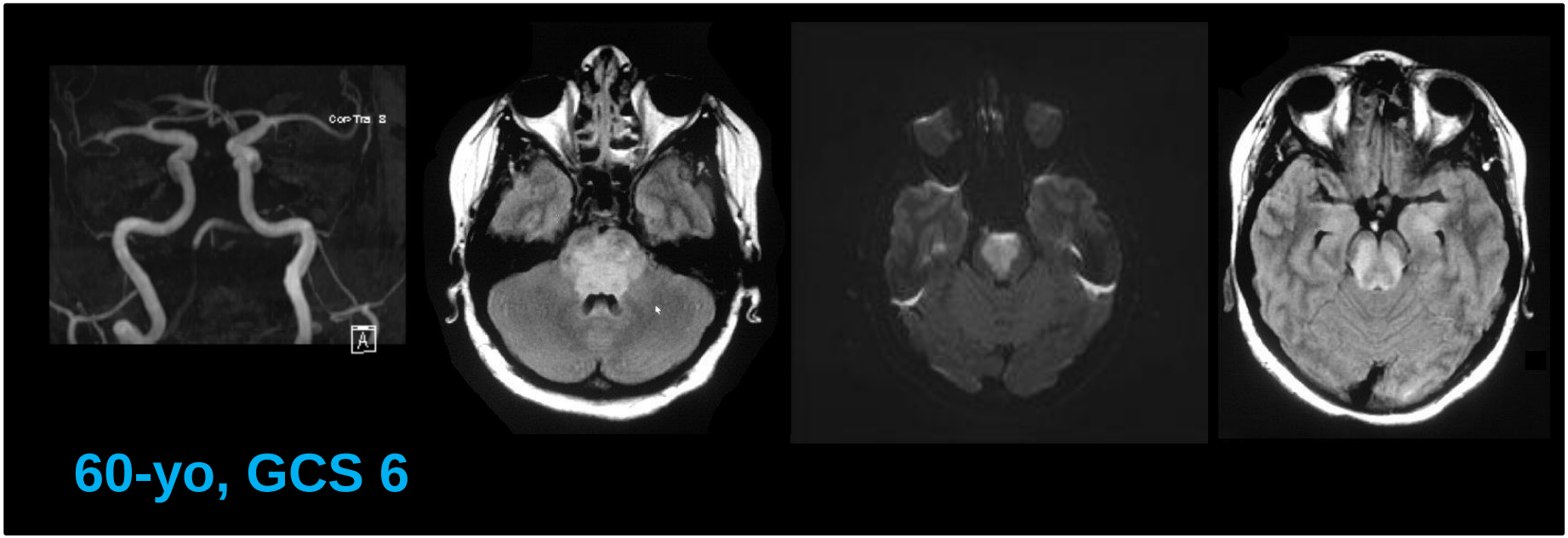


Posterior Circulation



BA-occlusion:
Mortality 80-90%



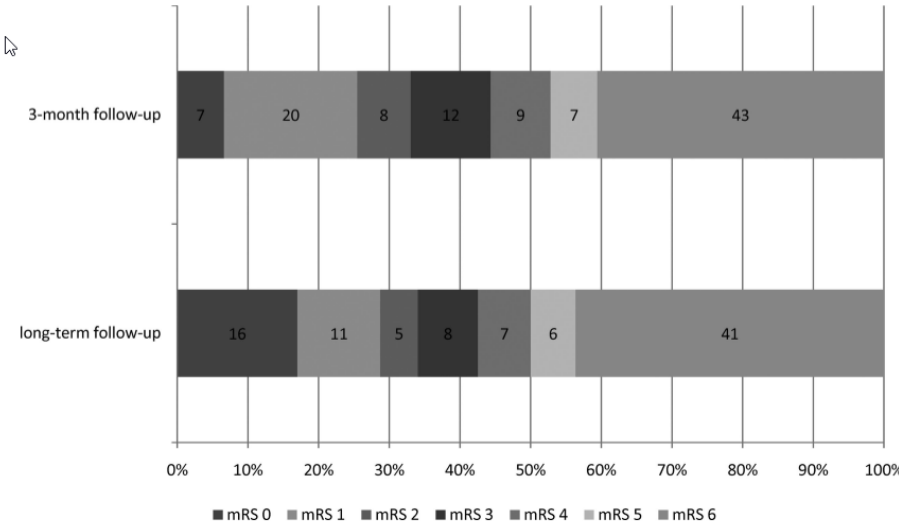


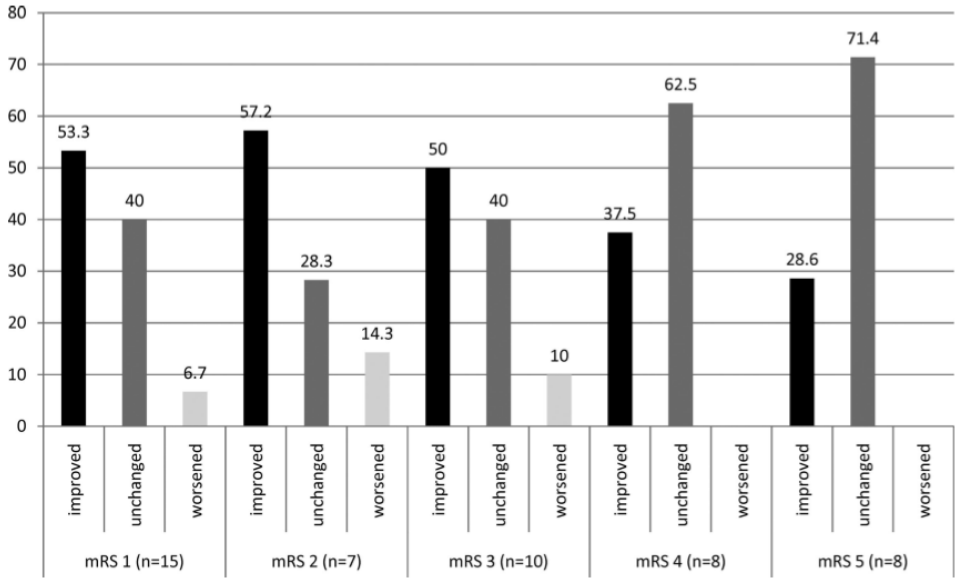
60-yo, GCS 6

Three-Month and Long-Term Outcomes and Their Predictors in Acute Basilar Artery Occlusion Treated With Intra-Arterial Thrombolysis

Simon Jung, MD; Marie-Luise Mono, MD; Urs Fischer, MD; Aekaterini Galimanis, MD; Oliver Findling, MD; Gian Marco De Marchis, MD; Anja Weck, MD; Krassen Nedeltchev, MD; Giuseppe Colucci, MD; Pasquale Mordasini, MD; Caspar Brekenfeld, MD; Marwan El-Koussy, MD; Jan Gralla, MD, MSc; Gerhard Schroth, MD; Heinrich P. Mattle, MD; Marcel Arnold, MD

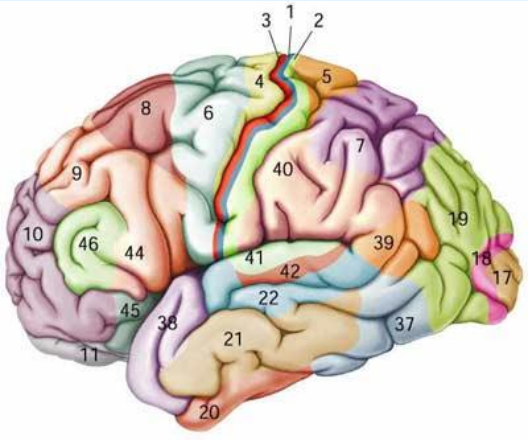
- Median time from stroke to long-term follow-up 37.6 months
- Range 1-11.8 years

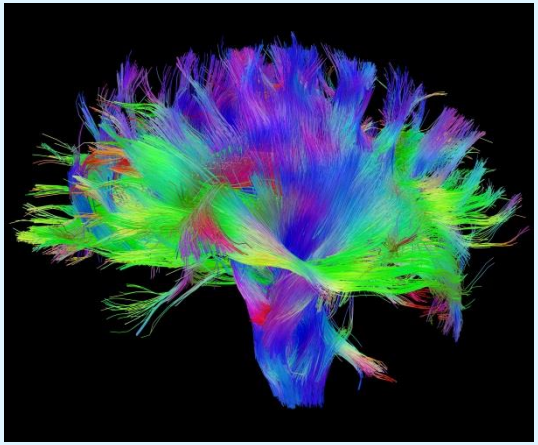


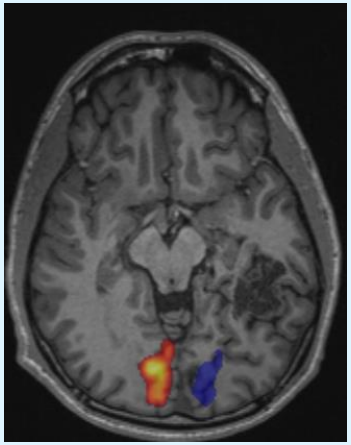


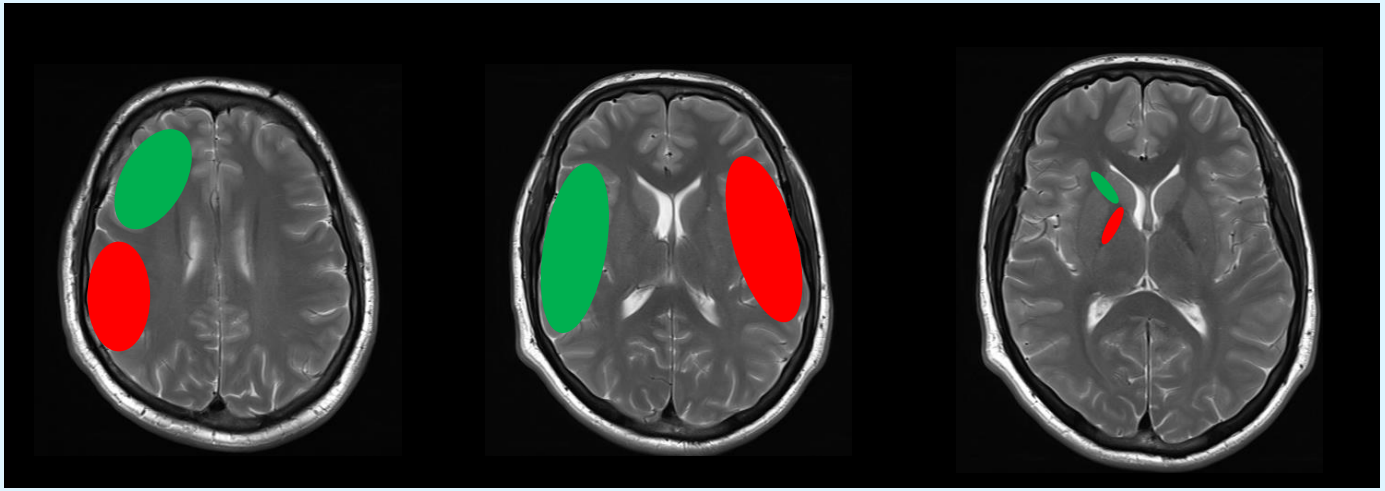
- There is a recovery potential beyond 3 months for many patients!

Is the relevant unit for brain tissue *ml*?









The role of IVT in patients undergoing mechanical thrombectomy

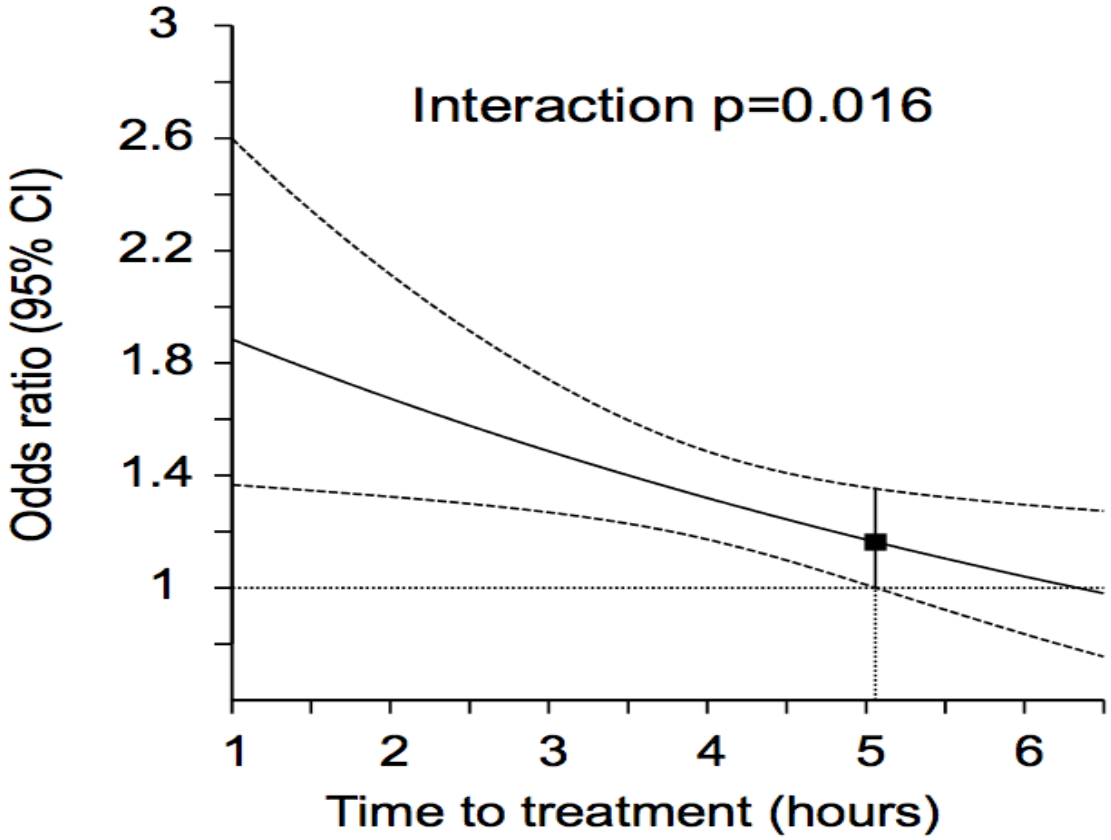
Intra-venous thrombolysis is effective and safe in:

- All ethnic groups (Mishra Int J Stroke 2014)
- Dissections (Zinkstok Stroke 2011)
- Posterior circulation stroke (Sarikaya Stroke 2011)
- Recent stroke >6 weeks (Multiple studies)
- Minor silent subacute stroke (Tisserand Neurol 2011; Gaillard AJNR 2012)
- Severe hypertension (IST-3, Wardlaw Lancet 2012)
- Glucose ↑↓ (IST-3, Wardlaw Lancet 2012)
- INR up to 1.7 (Mazyna/VISTA Ann Neurol 2013)
- Recent MI > 7 weeks (Da Silva Neurology 2011)
- Seizures (if stroke proven radiologically)
- Asymptomatic aneurysms (Edwards Stroke 2012; Sheth Neurocirt Care 2012)
- Moderate leukoaraiosis (Neumann-Haefelin Stroke 2005)
- Morderate microbleeds (Fiehler Stroke 2007; Shoamanesh Int J Stroke 2013)

Limitations of IVT

1) Rapidly decreasing efficacy

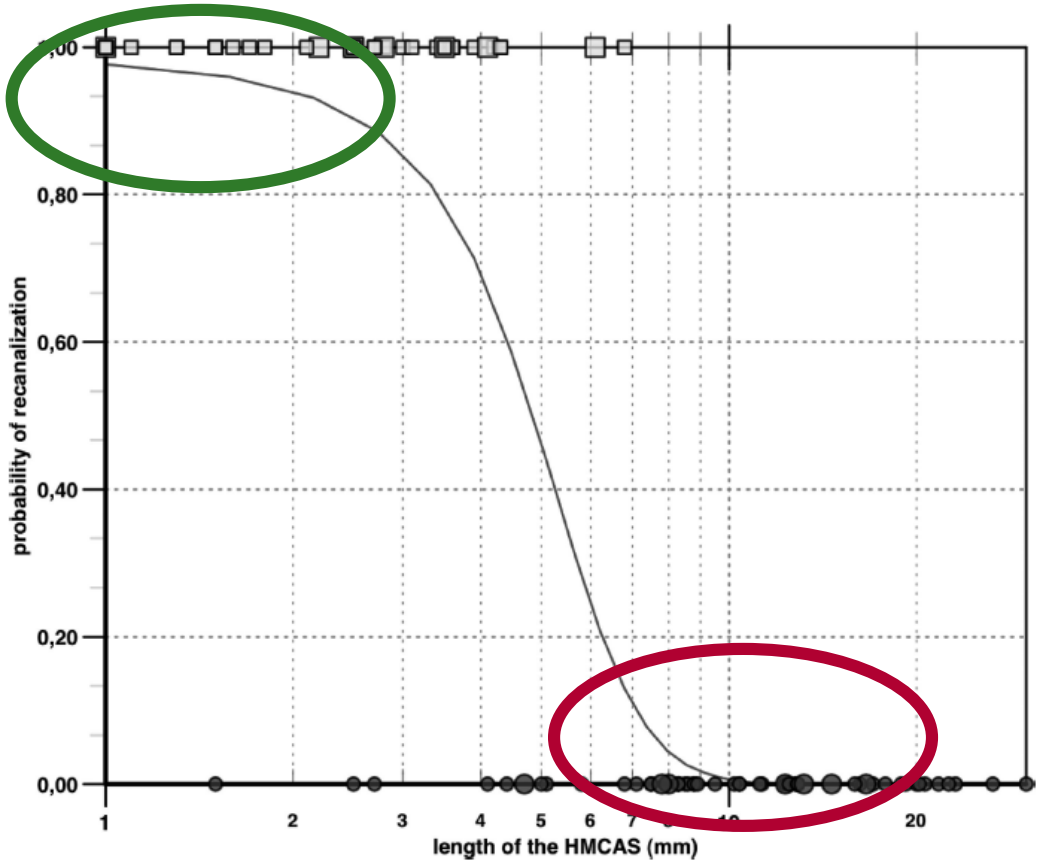
ECASS, ATLANTIS, NINDS, EPITHET and IST-3 trials.
Effect on mRS 0-1 by treatment delay



	NNT
0-90 Min.	4.5
90-180 Min	9
180-270 Min	14.1

Emberson/STTC, Lancet 2014

2) Poor recanalization rate in large thrombi



Riedel et al. Stroke 2011

3) Further limitations

- Wake-up and siesta stroke
- Absolute and relative contraindications (warfarin, NOACs, surgery, systemic bleeding, high blood pressure etc.)
- Use of IA thrombolysis / antiplatelets / heparin after IVT limited

Is IVT beneficial prior to mechanical thrombectomy?

Is IVT always necessary?

Arguments pro bridging

1. rtPA can be started earlier («ship-and-drip»)
2. rtPA may facilitate recanalization (enzymatic digestion)
3. rtPA may improve reperfusion of small vessels (lysis of smaller distal thrombus fragments, microvascular thrombosis)
4. Mechanical thrombectomy may be delayed or not feasible

Arguments against bridging

1. rtPA poor recanalization rates in large vessel occlusion
2. rtPA narrow time window with decreasing efficacy
3. rtPA absolute/relative contraindications
4. rtPA (relative) contraindication for IA lytics/antiplatelets/heparin
5. rtPA increases risk of hemorrhage
6. rtPA may produce thrombus dislocation
7. rtPA impact on health care costs
8. rtPA may cause life-threatening complications
9. rtPA may delay EVT in some patients

Two cohorts of patients

„Drip & Ship“

„Mothership“

Stroke Unit

IVT

Stroke Center

IVT

MT

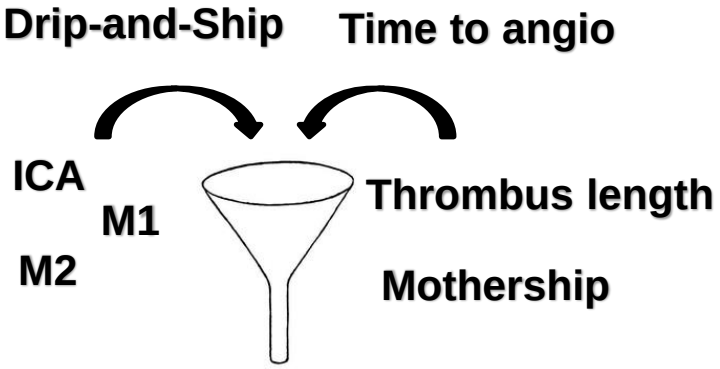
Major arguments

1) **Preinterventional Reperfusion**

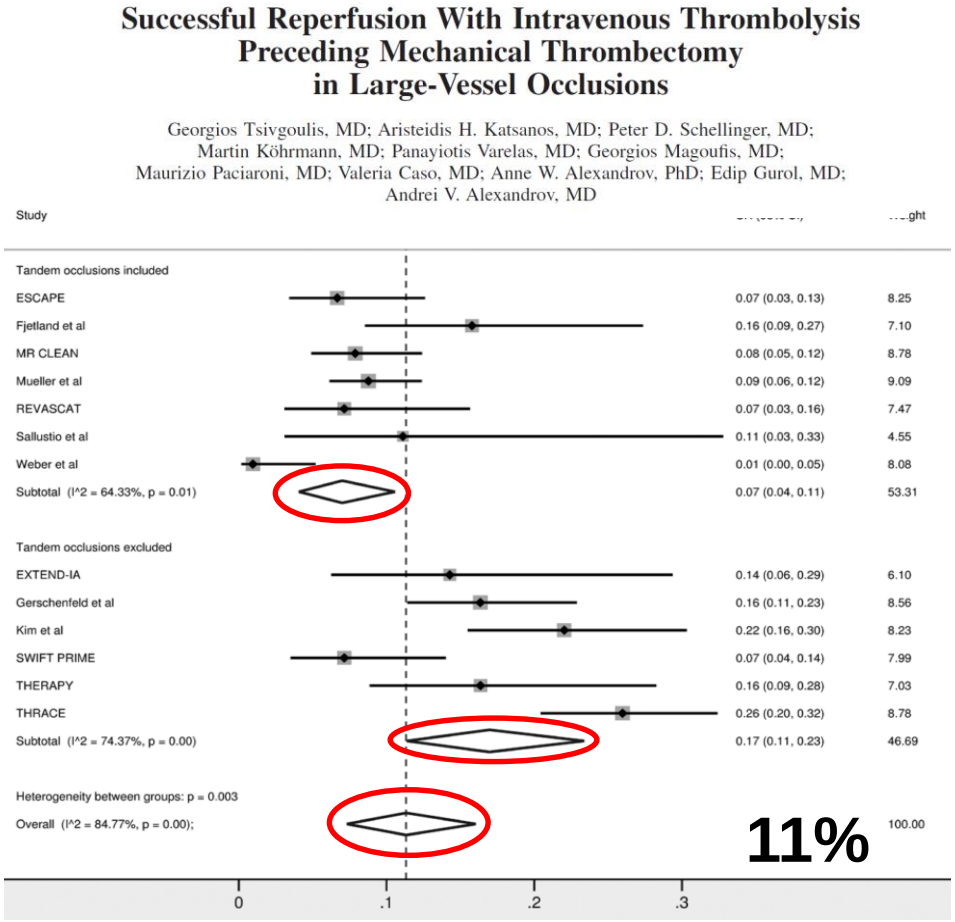
2) Reperfusion Success

3) Symptomatic Intracerebral Hemorrhage

1. Preinterventional Reperfusion Prevalence

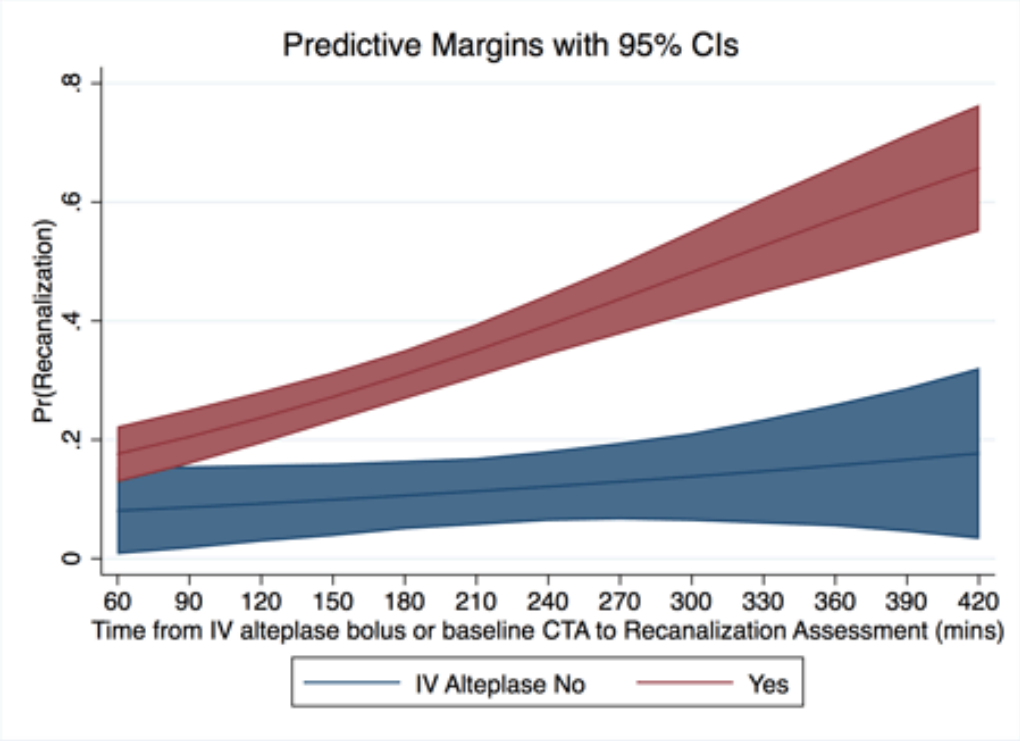


Prevalence of reperfusion prior to EVT

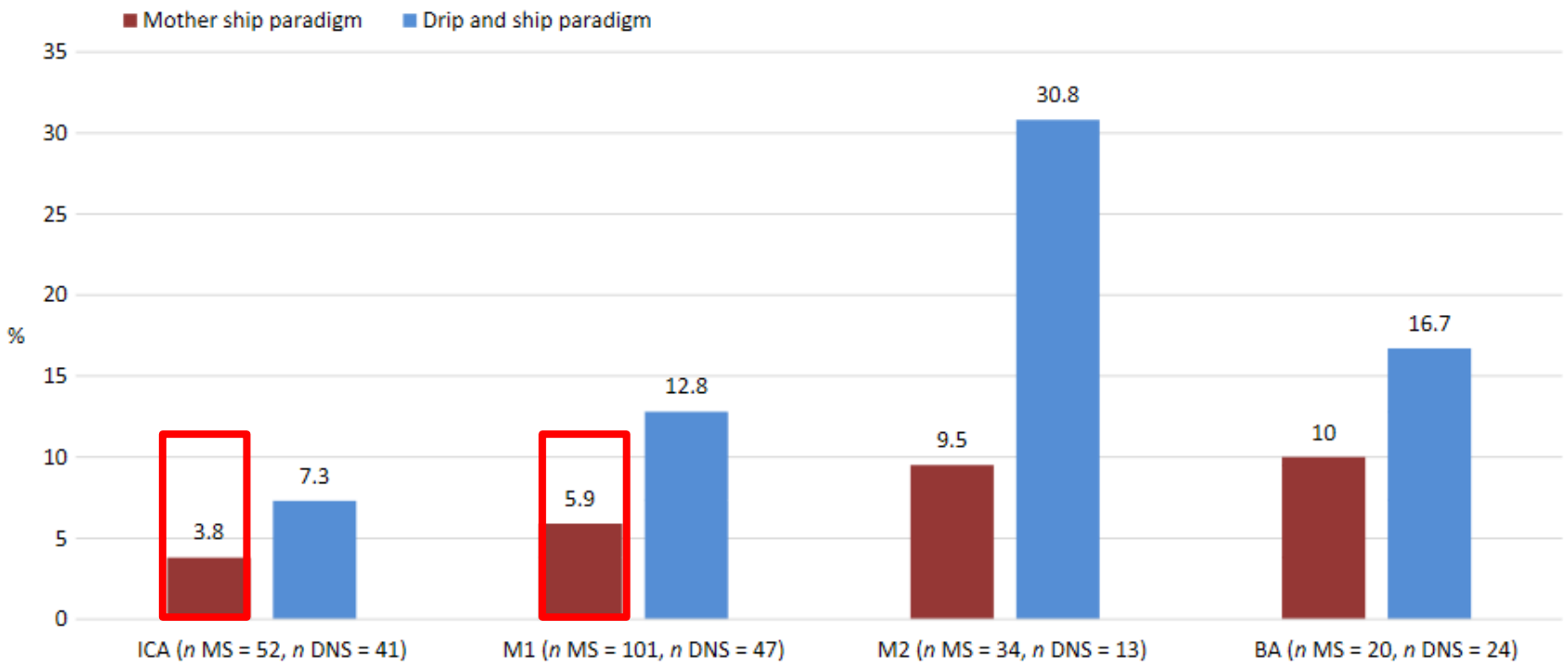


Pre-treatment with rtPA in LVO stroke eligible for mTE results in successful reperfusion in 1 of 10 cases.

Time dependence of preinterventional reperfusion



1. Preinterventional Reperfusion
Time dependency

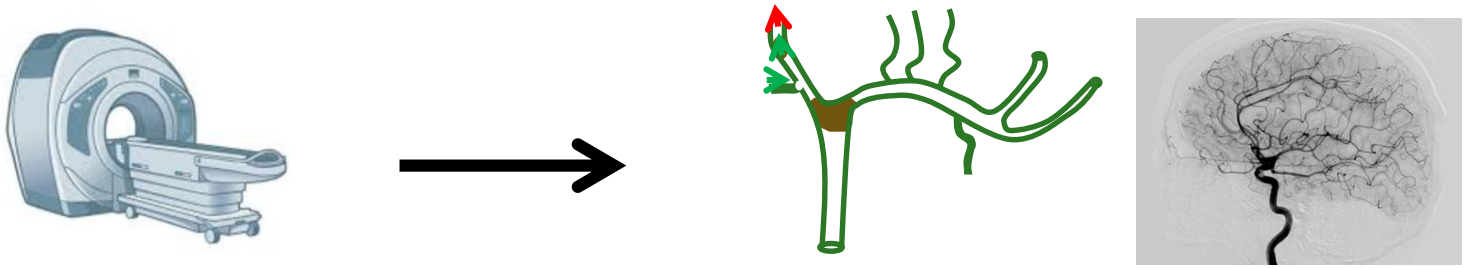


Mueller et al. EJON 2017

1. Preinterventional Reperfusion What about mothership only?

Rates and Quality of Preinterventional Reperfusion in Patients With Direct Access to Endovascular Treatment

Johannes Kaesmacher, MD; Mattia Giarrusso, MD; Felix Zibold, MD; Pascal J. Mosimann, MD; Tomas Dobrocky, MD; Eike Piechowiak, MD; Sebastian Bellwald, MD; Marcel Arnold, MD; Simon Jung, MD; Marwan El-Koussy, MD; Pasquale Mordasini, MD; Jan Gralla, MD*; Urs Fischer, MD*



Overall **change of occlusion site (COS)** 10.7% in 720 endovascular candidates, subdividing into:

- 2.7% COS with TICI 0/1
- 6.2% COS with ≥TICI 2a (including 2.9% with TICI≥2b)
- 1.8% COS with perfusion worsening

Kaesmacher et al. Stroke 2018

Major arguments

1) Preinterventional Reperfusion

2) Reperfusion Success

3) Symptomatic Intracerebral Hemorrhage

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

Johannes Kaesmacher,[1,2] Pasquale Mordasini,[2] Marcel Arnold,[1] Elena López-Cancio,[3] Neus Cerdá,[4] Tobias Boeckh-Behrens,[5] Justus F Kleine,[6] Mayank Goyal,[7] Michael D Hill,[8] Vitor Mendes Pereira,[9] Jeffrey L Saver,[10] Jan Gralla,[2] Urs Fischer[1]

IVT + MT vs dMT

- **dMT in IVT eligible pts**
- **dMT in IVT ineligible pts**

- Meta-analysis including 20 studies with 5279 patients

Direct MT vs bridging approach in mothership patients

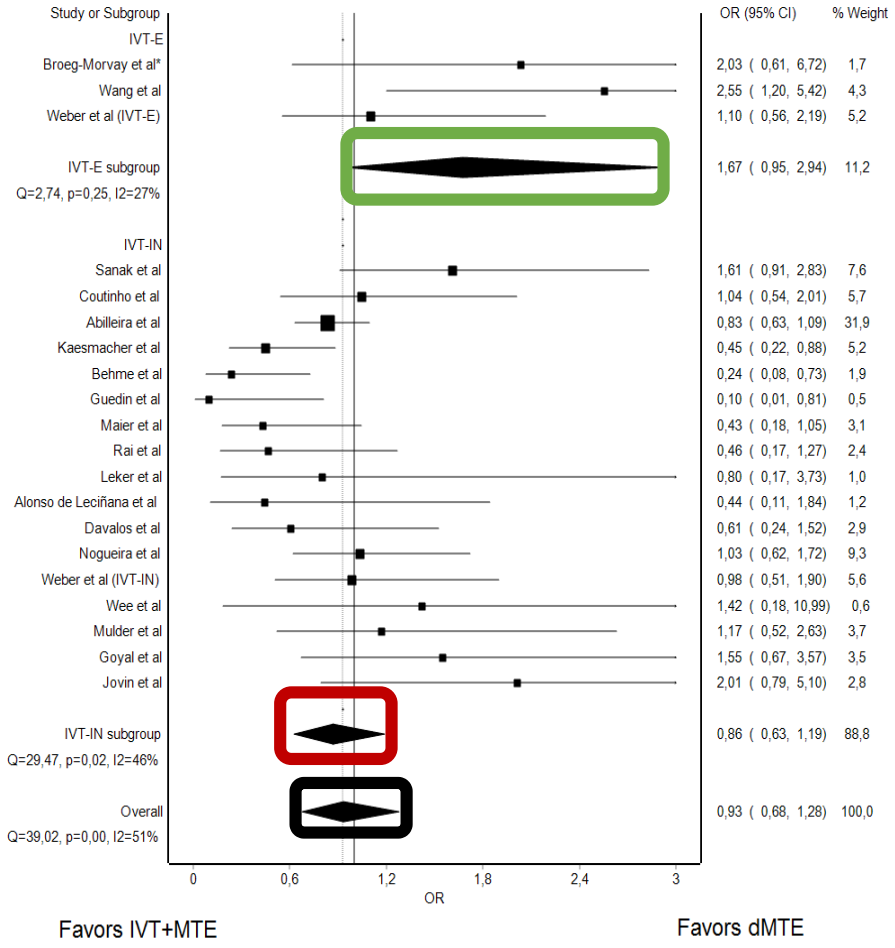
Comparison of baseline factors and risk factor profile:

- Comparable age and admission NIHSS

- dMTE patients had higher odds for:
  - **atrial fibrillation** (1.94, 95%-CI 1.50-2.50)
  - **prior cerebrovascular events** (1.94, 95%-CI 1.60-2.35)

- dMTE patients were treated **later**

2. Reperfusion Success
TICI 2b/3



- **19/20 studies**
- **4220 patients**

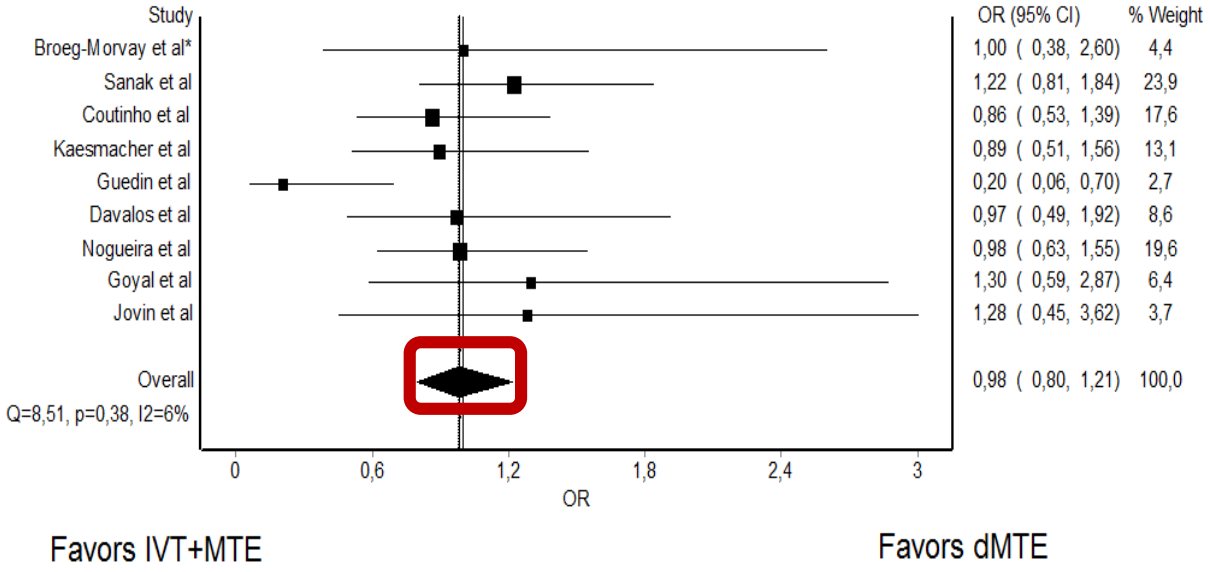
IVT-eligible dMTE patients

IVT-ineligible dMTE patients

- Overall, non-significant different rates of successful reperfusion
- Non-significant trend for higher rates of successful reperfusion in IVT eligible pts.

Kaesmacher et al. JNIS 2018

2. Reperfusion Success
TICI 3



- **9/20 studies**
- **1753 patients**

→ no effect

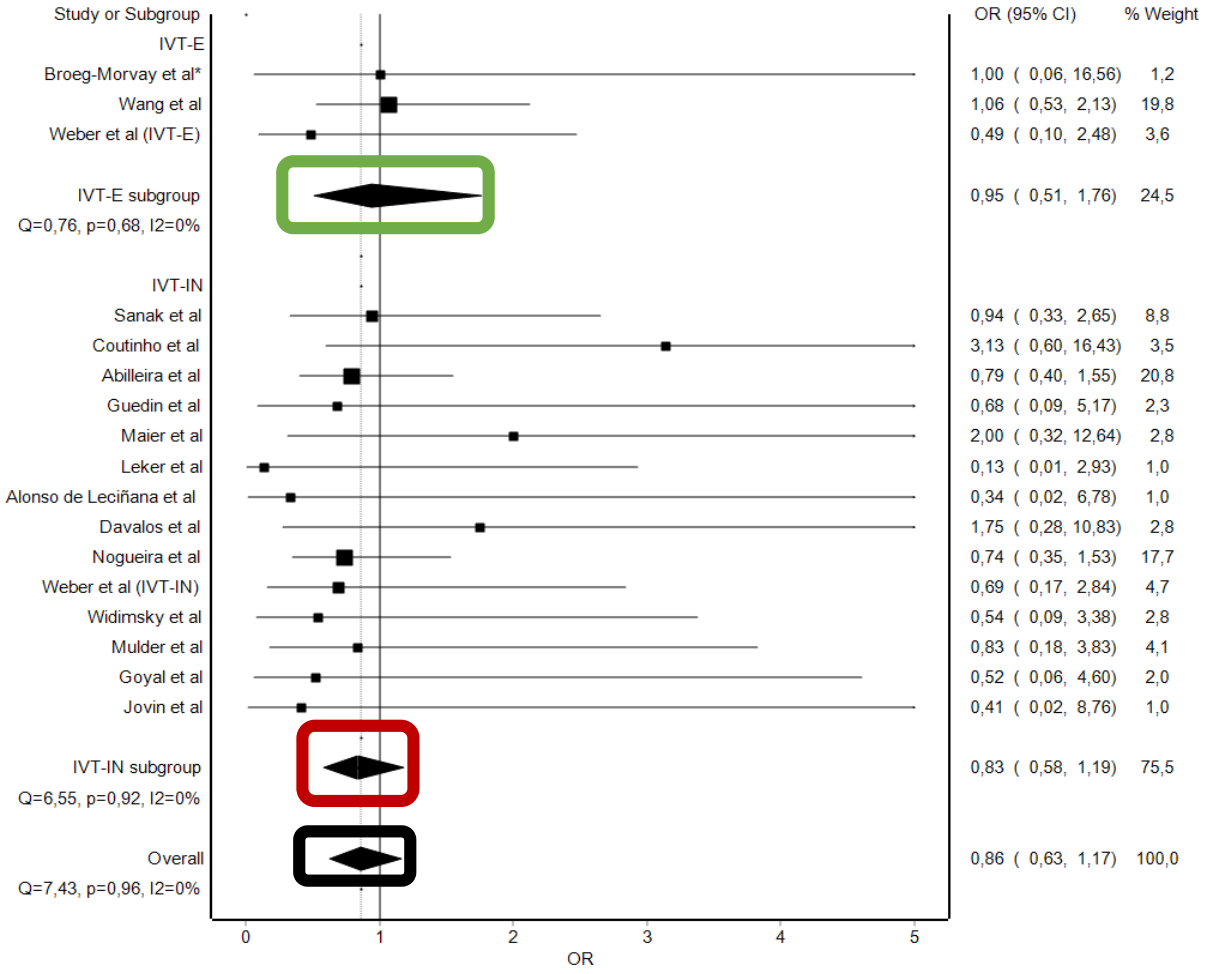
Major arguments

1) Preinterventional Reperfusion

2) Reperfusion Success

3) Symptomatic Intracerebral Hemorrhage

3. Symptomatic ICH



- **16/20 studies**
- **3903 patients**

IVT-eligible dMTE patients

IVT-ineligible dMTE patients

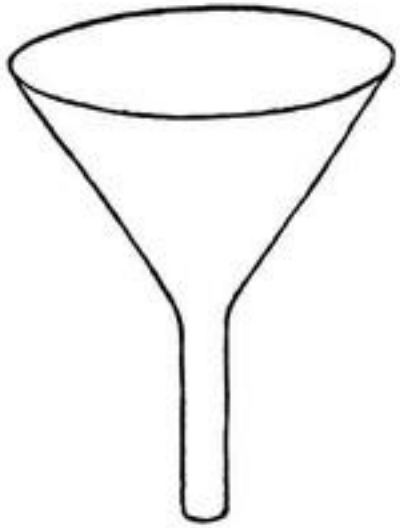
- Overall, non-significant trend for higher rates of sICH in IVT + MTE
- No treatment group effect

Kaesmacher et al. JINS 2018

Preinterventional Reperfusion

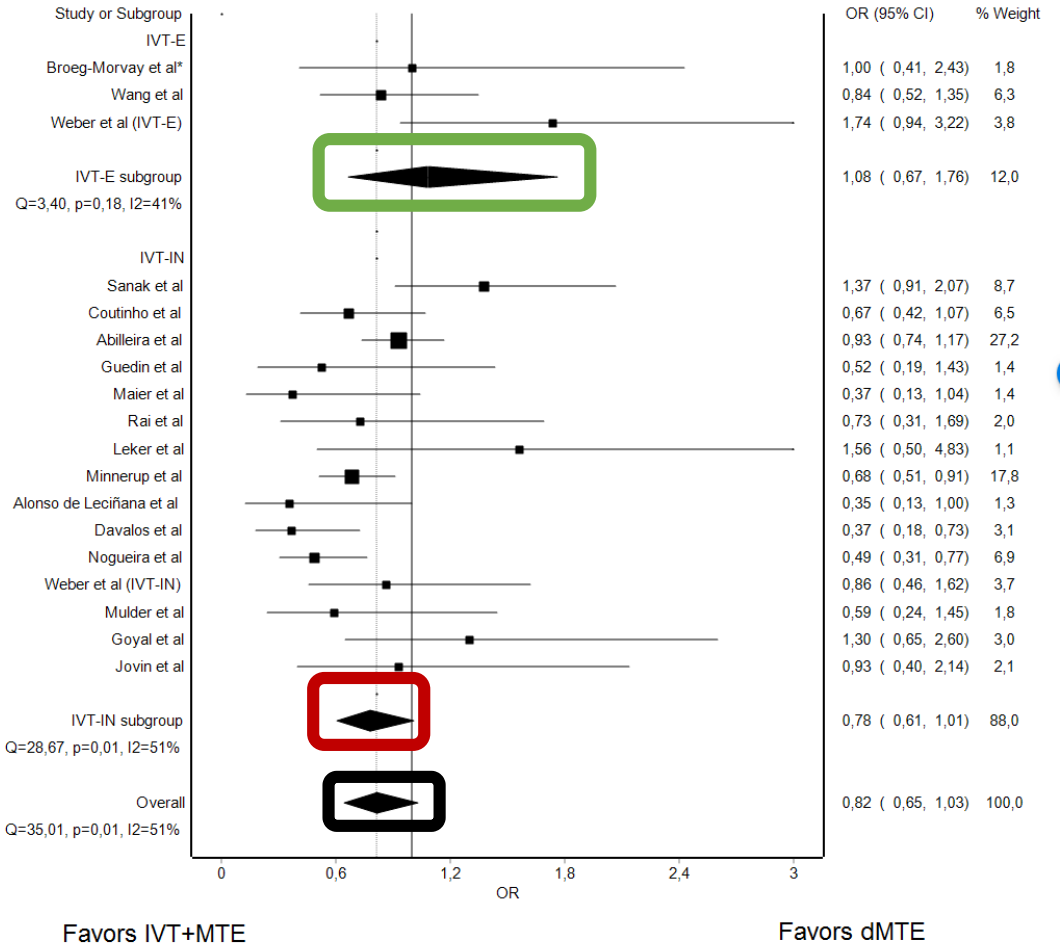
Reperfusion Success

Symptomatic ICH



Outcome?

Outcome
Functional independence



- **17/20 studies**
- **4657 patients**

IVT-eligible dMTE patients

IVT-ineligible dMTE patients

- Overall, non-significant trend for lower rates of functional outcome in dMT
- dMT IVT-E: no difference in rates of functional outcome
- dMT IVT-IN: non-significant trend for lower rates of functional outcome

Kaesmacher et al. JNIS 2018

Individualized decision against t-PA?

- Mothership (Angio team ready)

  → **Time dependency of IVT efficacy !**

- Carotid-T, large thrombi

  →**low efficacy + risk of perfusion worsening**

- Microbleeds, striatal infarction, diabetic, high ASPECTS

  → **sICH**

- Tandem → **sICH, antiplatelet medication**

Summary

- It is not possible to ***reliably*** prevent/predict “futile recanalization” in an individual stroke patient!

- However, the question is not, whether a patient has the potential to achieve a mRS 0-2, ***BUT*** whether EVT has the ***potential to reduce morbidity (shift in mRS)*** with a justifiable interventional risk in the individual patient setting

- ***IVT*** will remain the ***standard of care*** for all patients with ***peripheral intracranial vessel occlusion and drip-and-ship***, but a trial is needed comparing ***direct mechanical thrombectomy*** versus bridging thrombolysis in patients with LVO in the anterior circulation and whom can ***immediately*** be treated by EVT

- For the time being:
  ➡ ***Broad selection criteria for thrombectomy!***
  ➡ ***Reduce overselection*** ➡ ***In doubt – treat!***