Evidence and potential implications of the 6 – 24h EVT treatment window for AIS

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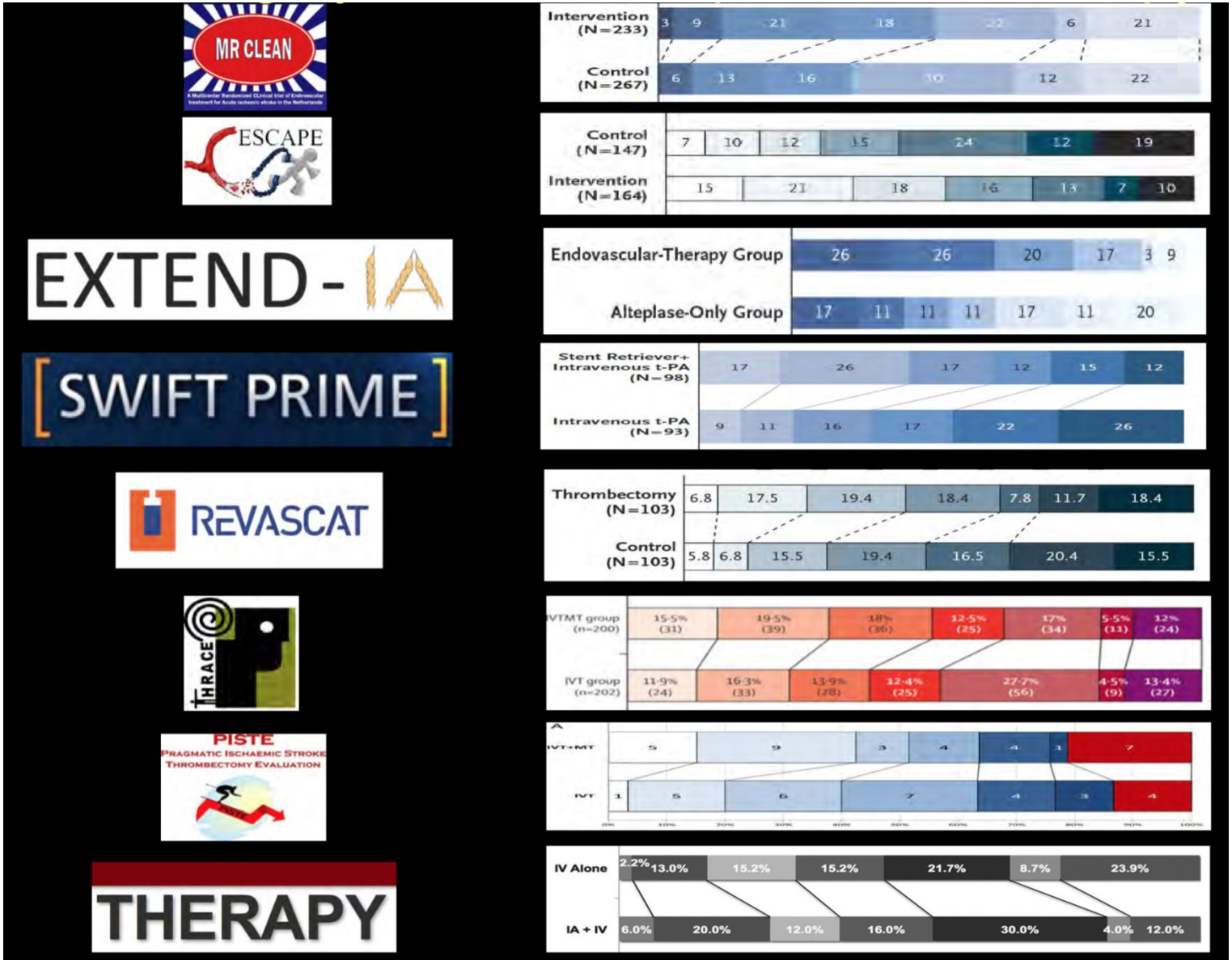
Disclosure Statement of Financial Interest

Affiliation/Financial Relationship

- Global PI of STAR trial
- Interventional Principal Investigator of SWIFT-PRIME Trial (Medtronic sponsored trial)
- North America Principal Investigator of SWIFT-DIRECT Trial (Medtronic sponsored trial)
- Consultant for Penumbra (PROMISE trial), and Stryker (DAWN trial, TREVO registry), Neurovasc Med (start up), Marblehead (start up)

2015-2018: Highly effective reperfusion therapies



HERMES collaboration

- 5 trials published in early 2015
  - MRCLEAN
  - ESCAPE
  - SWIFTPRIME
  - EXTEND IA
  - REVASCAT
- All supported endovascular thrombectomy as a definitive treatment for anterior circulation, large vessel occlusive ischemic stroke
- Pooled analyses of individual patient data will allow:
  - Greater precision
  - Analysis of subgroups

Methods

- A literature review confirmed that 5 major trials examining modern endovascular stroke treatment were published at the time of analysis
- A mixed effects model, with study as a random variable was used to assess the treatment effect across the 5 studies
- Sub-groups of interest were age, sex, occlusion location, ASPECTS score, treatment with alteplase and time from randomization

Baseline Characteristics
(N=1287)

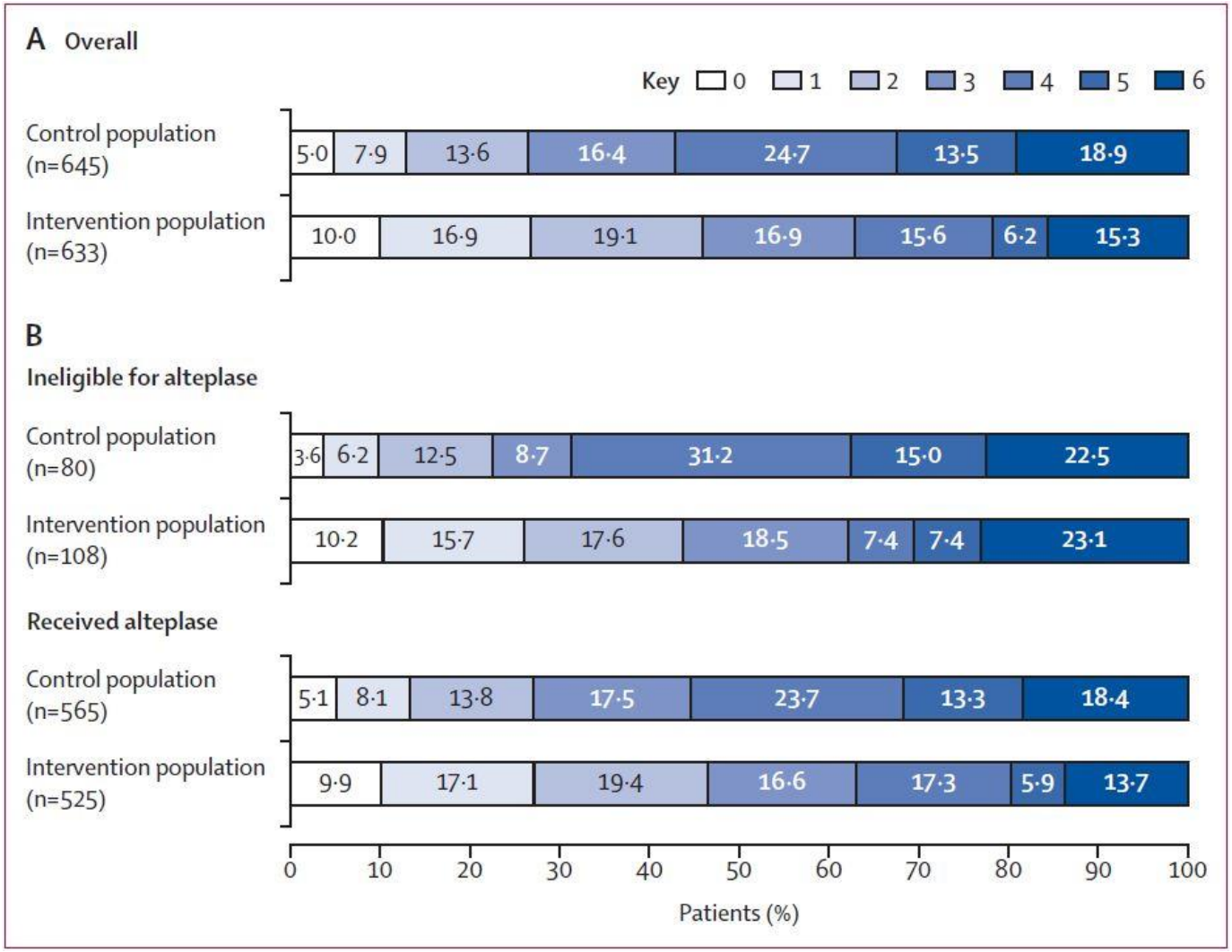
	Intervention population (n=634)	Control population (n=653)
Demographic characteristics		
Median age (years)	68 (57–77)	68 (59–76)*
Men	330 (52%)	352 (54%)
Women	304 (48%)	301 (46%)
Past medical history		
Hypertension	352 (56%)	388 (59%)
Diabetes mellitus	82 (13%)	88 (13%)
Atrial fibrillation	209 (33%)	215 (33%)
Smoking (recent or current)	194 (31%)	210 (32%)
Clinical characteristics		
Baseline NIHSS score	17 (14–20))†	17 (13–21)‡
Baseline blood glucose (mmol/L)	6·6 (5·9–7·8)§	6·7 (5·9–7·8)¶

Baseline Characteristics

Imaging characteristics		
ASPECTS on baseline CT	9 (7–10)§	9 (8–10)¶
Intracranial occlusion location		
Internal carotid artery	133 (21%)	144 (22%)
M1 segment middle cerebral artery	439 (69%)	452 (69%)
M2 segment middle cerebral artery	51 (8%)	44 (7%)
Others	11 (2%)	13 (2%)
Treatment details and process times		
Treatment with intravenous alteplase	526 (83%)	569 (87%)
Treatment with intravenous alteplase documented within 180 min	442 (70%)	462 (71%)
Process times (min)		
Onset to randomisation	195·5 (142–260)‖	196 (142–270)*
Onset to intravenous alteplase	100 (75–133)**	100 (74–140)††
Onset to reperfusion	285 (210–362)	NA

Data are median (IQR), n (%), or mean (SD)· NIHSS=National Institute of Health Stroke Scale· ASPECTS=Alberta Stroke Program Early CT Score· *n=650· †n=631· ‡n=648· §n=620· ¶n=644· ‖n=632· **n=598· ††n=618·

Overall Treatment Effect
NNT = 2.6



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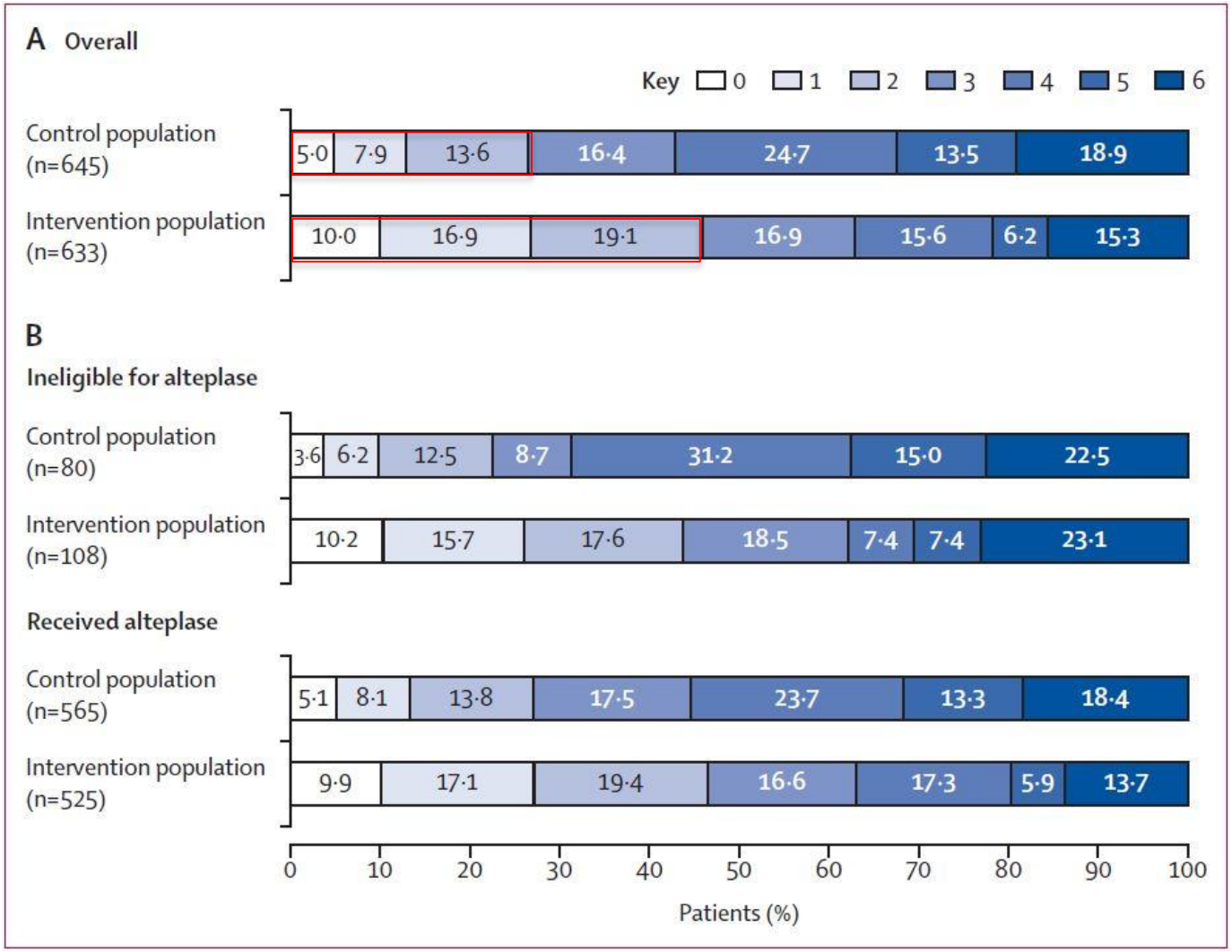
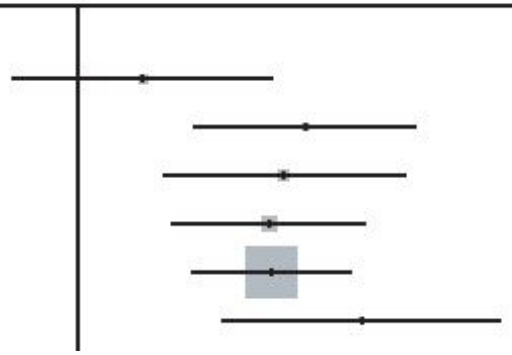


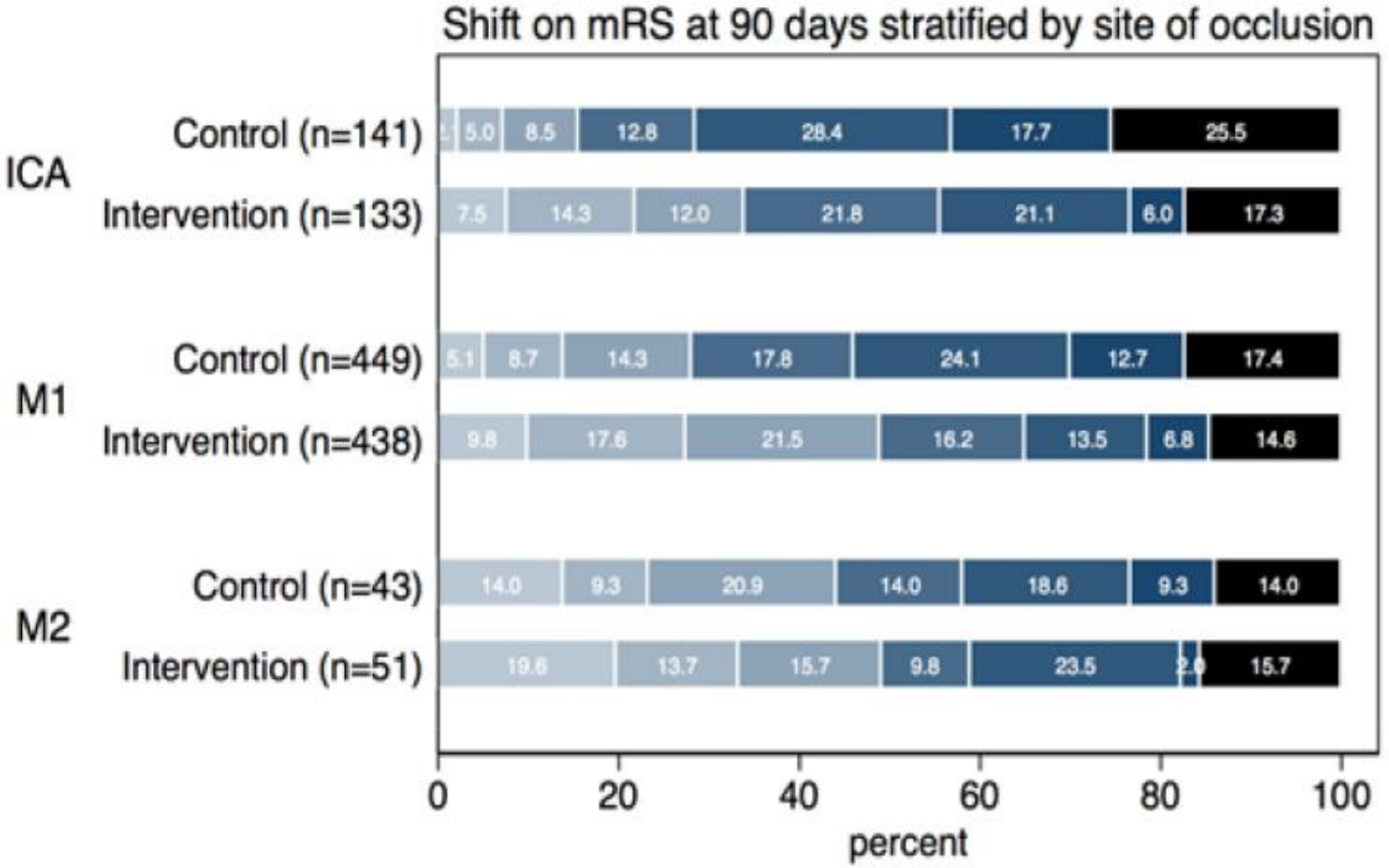
Treatment effect by age

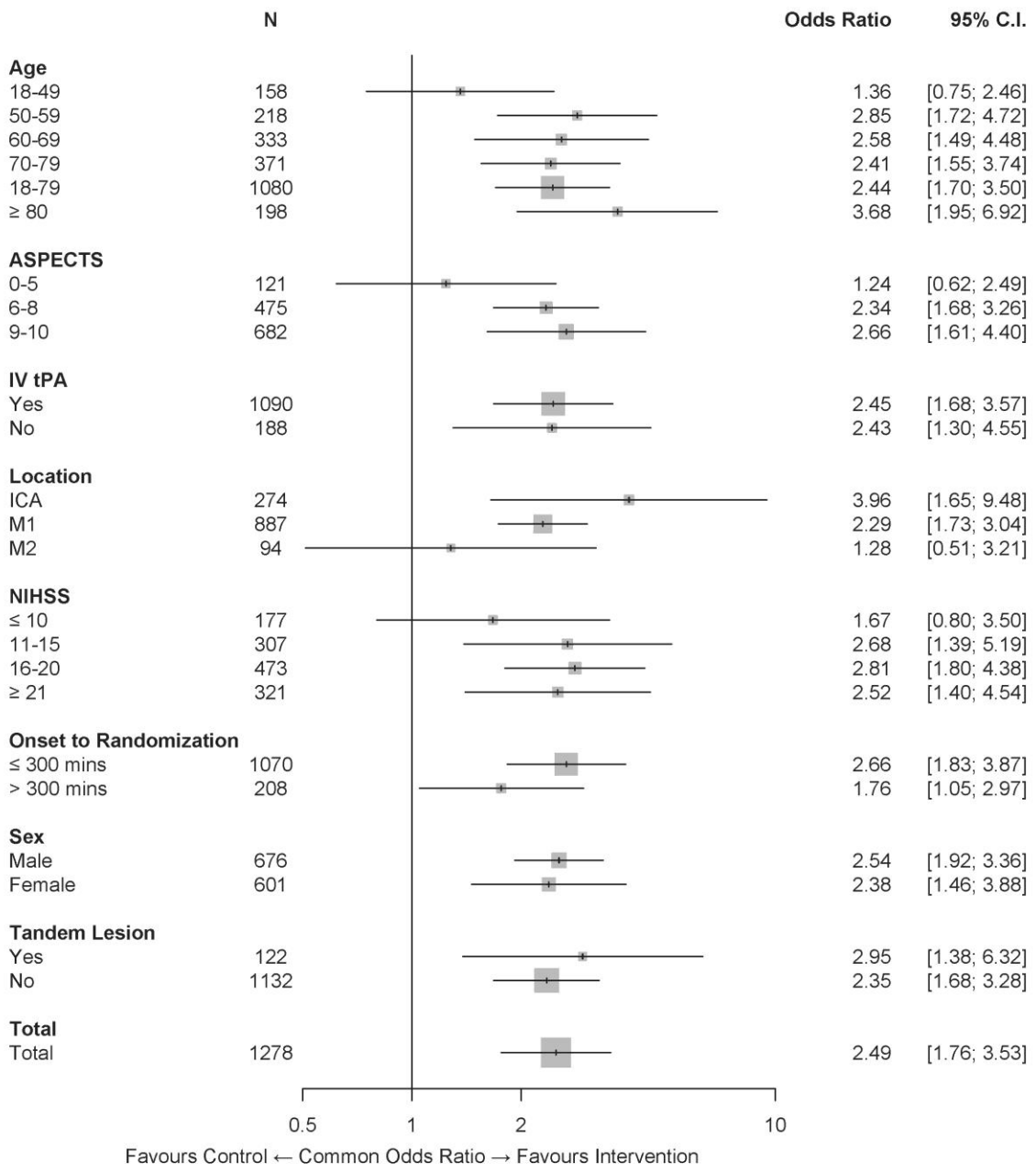
mRS 0-2 at 90 days

	n	cOR (95% CI)
Age (years) ($p_{interaction} = 0{\cdot}07$)		
18–49	158	1·36 (0·75–2·46)
50–59	218	2·85 (1·72–4·72)
60–69	333	2·58 (1·49–4·48)
70–79	371	2·41 (1·55–3·74)
18–79	1080	2·44 (1·70–3·50)
≥80	198	3·68 (1·95–6·92)



Treatment effect is strong across occlusion sites (p_{int}=0.35)

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95% C.I.
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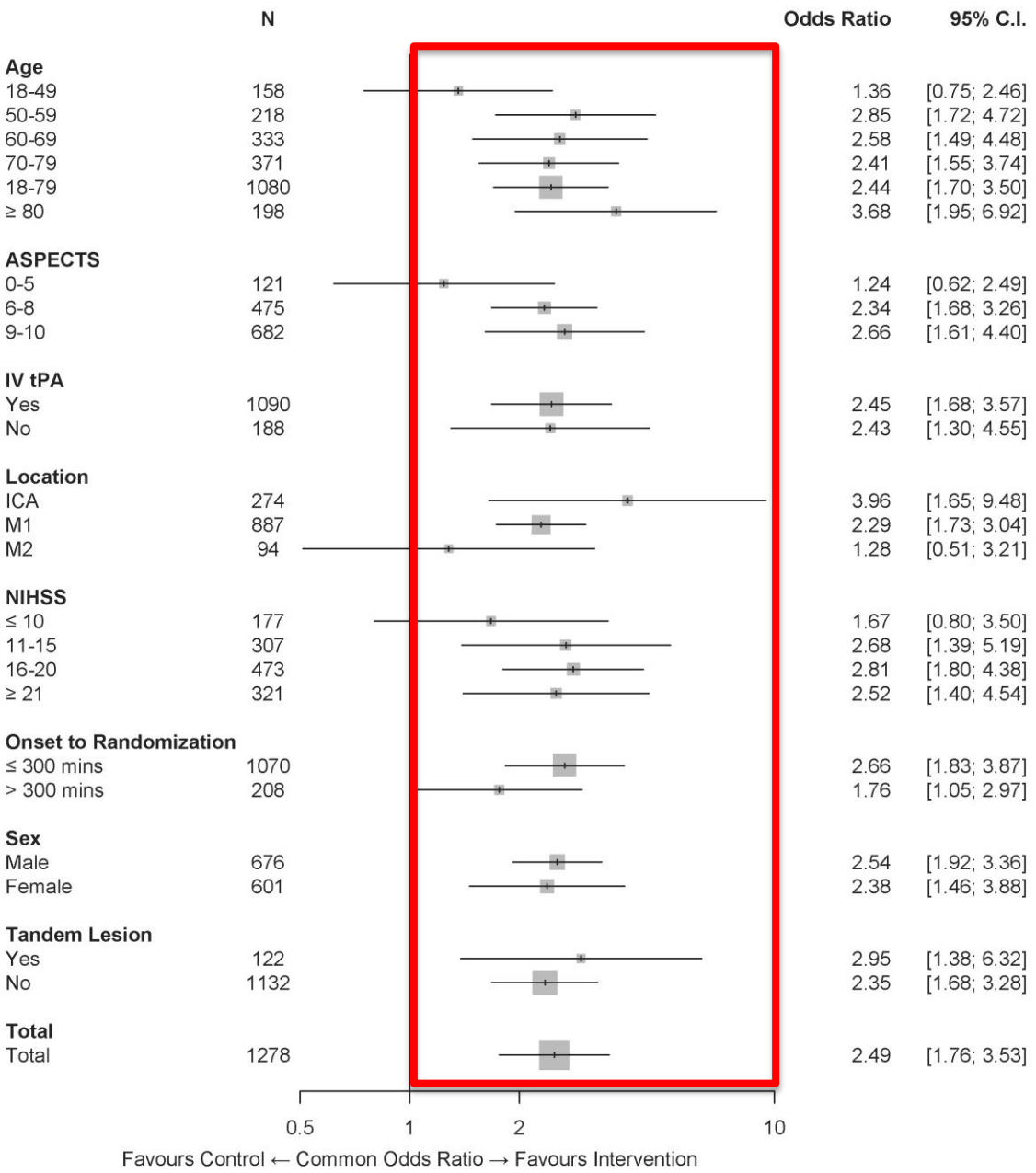
≥ 80 198 3.68 [1.95; 6.92]
ASPECTS
0-5 121 1.24 [0.62; 2.49]
6-8 475 2.34 [1.68; 3.26]
9-10 682 2.66 [1.61; 4.40]
IV tPA
Yes 1090 2.45 [1.68; 3.57]
No 188 2.43 [1.30; 4.55]
Location
ICA 274 3.96 [1.65; 9.48]
M1 887 2.29 [1.73; 3.04]
M2 94 1.28 [0.51; 3.21]
NIHSS
≤ 10 177 1.67 [0.80; 3.50]
11-15 307 2.68 [1.39; 5.19]
16-20 473 2.81 [1.80; 4.38]
≥ 21 321 2.52 [1.40; 4.54]
Onset to Randomization
≤ 300 mins 1070 2.66 [1.83; 3.87]
> 300 mins 208 1.76 [1.05; 2.97]
Sex
Male 676 2.54 [1.92; 3.36]
Female 601 2.38 [1.46; 3.88]
Tandem Lesion
Yes 122 2.95 [1.38; 6.32]
No 1132 2.35 [1.68; 3.28]
Total
Total 1278 2.49 [1.76; 3.53]
0.5
1
2
10
Favours Control ← Common Odds Ratio → Favours Intervention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AHA Guidelines 2015

AHA/ASA Guideline

2015 AHA/ASA Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment

Endovascular Protocol and Patient Selection

"Patients eligible for intravenous rtPA should receive intravenous rtPA even if intra-arterial treatments are being considered."

Class I	Level of Evidence A	Unchanged Guideline

Patients should receive endovascular therapy with a stent retriever if they meet all the following criteria

a) prestroke mRS score 0 to 1,
b) acute ischemic stroke receiving intravenous r-tPA within 4.5 hours of onset according to guidelines from professional medical societies,
c) causative occlusion of the internal carotid artery or proximal MCA (M1),
d) age ≥18 years,
e) NIHSS score of ≥ 6,
f) ASPECTS of ≥ 6, and
g) treatment can be initiated (groin puncture) within 6 hours of symptom onset

Class I	Level of Evidence A	New Recommendation

Ovbiagele, and Dileep R. Yavagal. "2015 AHA/ASA Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association." American Heart Association Stroke Council. Stroke Published online June 29th 2015.

Canadian best practices 2015

4.3 Endovascular therapy

i. Endovascular therapy should be offered within a coordinated system of care including agreements with EMS; access to rapid neurovascular (brain and vascular) imaging; coordination between the ED, the stroke team and radiology; local expertise in neurointervention; and access to a stroke unit for ongoing management [Evidence Level A].

ii. Endovascular therapy is indicated in patients based upon imaging selection with noncontrast CT head and CTA (including extracranial and intracranial arteries) [Evidence Level A]. *See Appendix S4 for Inclusion Criteria for endovascular therapy.*

iii. Eligible patients who can be treated within six-hours (*i.e.* whose groin can be punctured within six-hours of symptom onset) should receive endovascular therapy [Evidence Level A]. *Refer to Appendix S4 for Inclusion Criteria for endovascular therapy.*

a. Select patients with disabling stroke presenting between 6 and 12 h of stroke symptom onset, including those with stroke symptoms upon awakening, who meet clinical and imaging criteria, may be considered for endovascular therapy [Evidence Level B], in accordance with local protocols.

Casaubon et al

Canadian best practices 2015

4.3 Endovascular therapy

i. Endovascular therapy should be offered within a coordinated system of care including agreements with EMS; access to rapid neurovascular (brain and vascular) imaging; coordination between the ED, the stroke team and radiology; local expertise in neurointervention; and access to a stroke unit for ongoing management [Evidence Level A].

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iii. Eligible patients who can be treated within six-hours (*i.e.* whose groin can be punctured within six-hours of symptom onset) should receive endovascular therapy [Evidence Level A]. *Refer to Appendix S4 for Inclusion Criteria for endovascular therapy.*

a. Select patients with disabling stroke presenting between 6 and 12 h of stroke symptom onset, including those with stroke symptoms upon awakening, who meet clinical and imaging criteria, may be considered for endovascular therapy [Evidence Level B], in accordance with local protocols.

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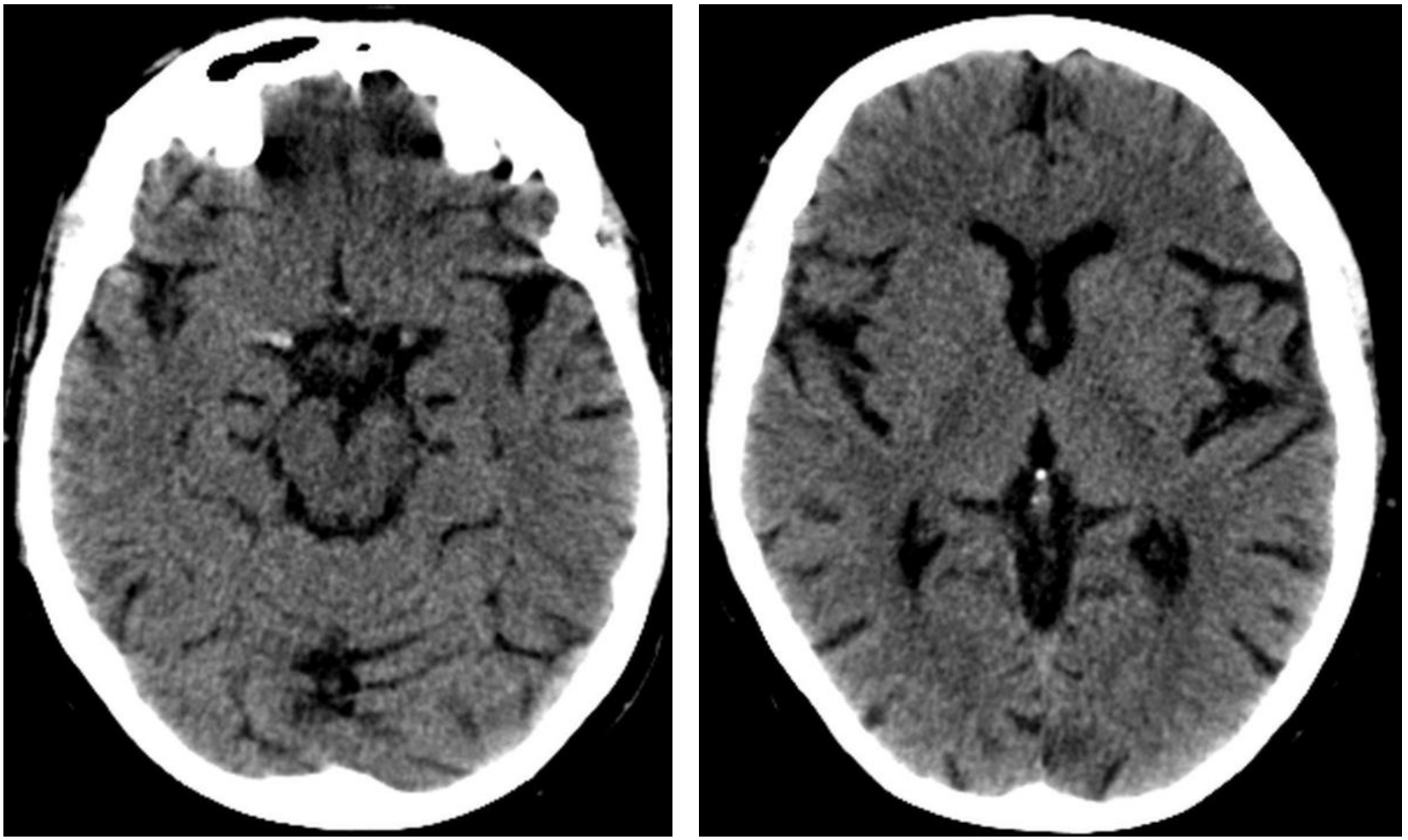
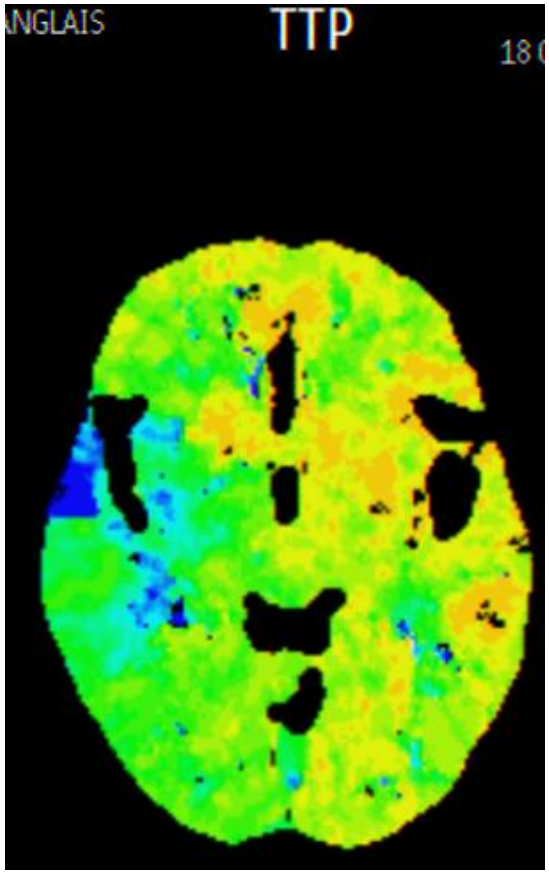
Case Discussion

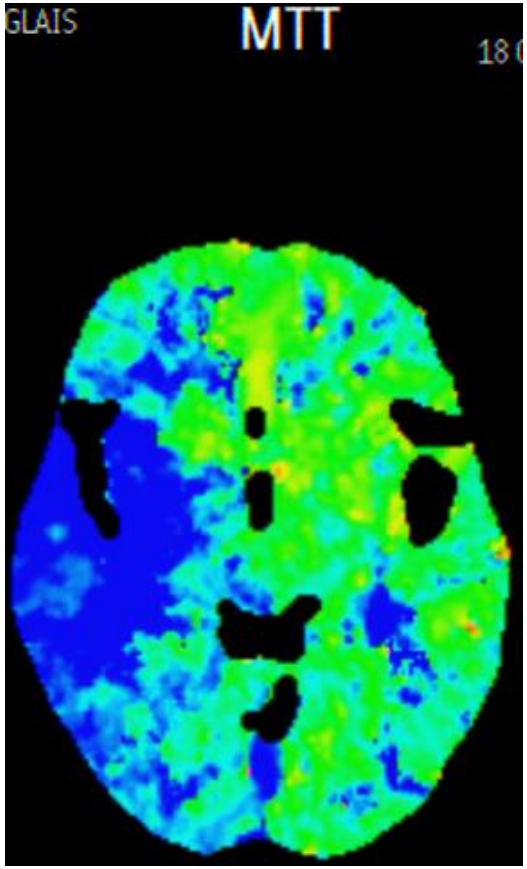
- 62y, F
- Time from stroke onset – 9h
- NIHSS – 18
- Afib

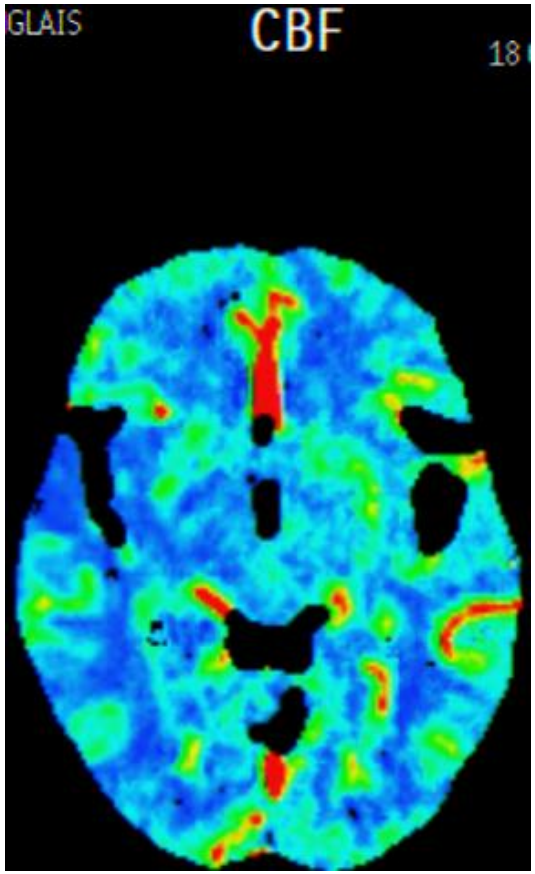
Baseline CT – Good ASPECTS (9-10)



CT Perfusion – Small core (20cc)







What would you do?

- Next EVT hospital was 2h away

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- Year 2013

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- Recommended transfer to an EVT center

What would you do?

- Next EVT hospital was 2h away
- Year 2013

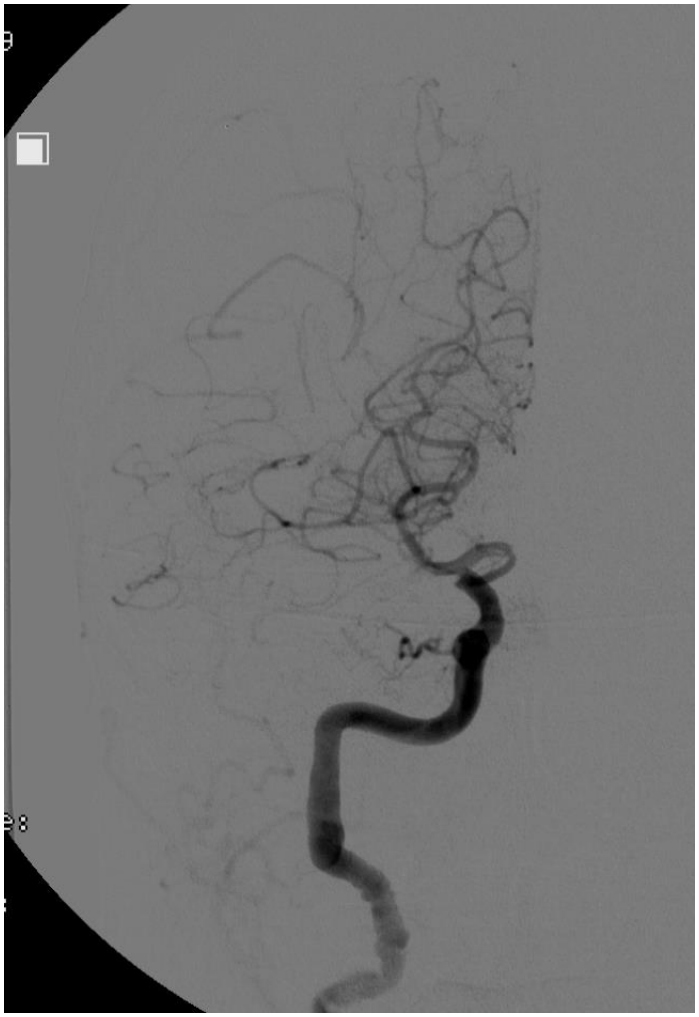
- Recommended transfer to an EVT center

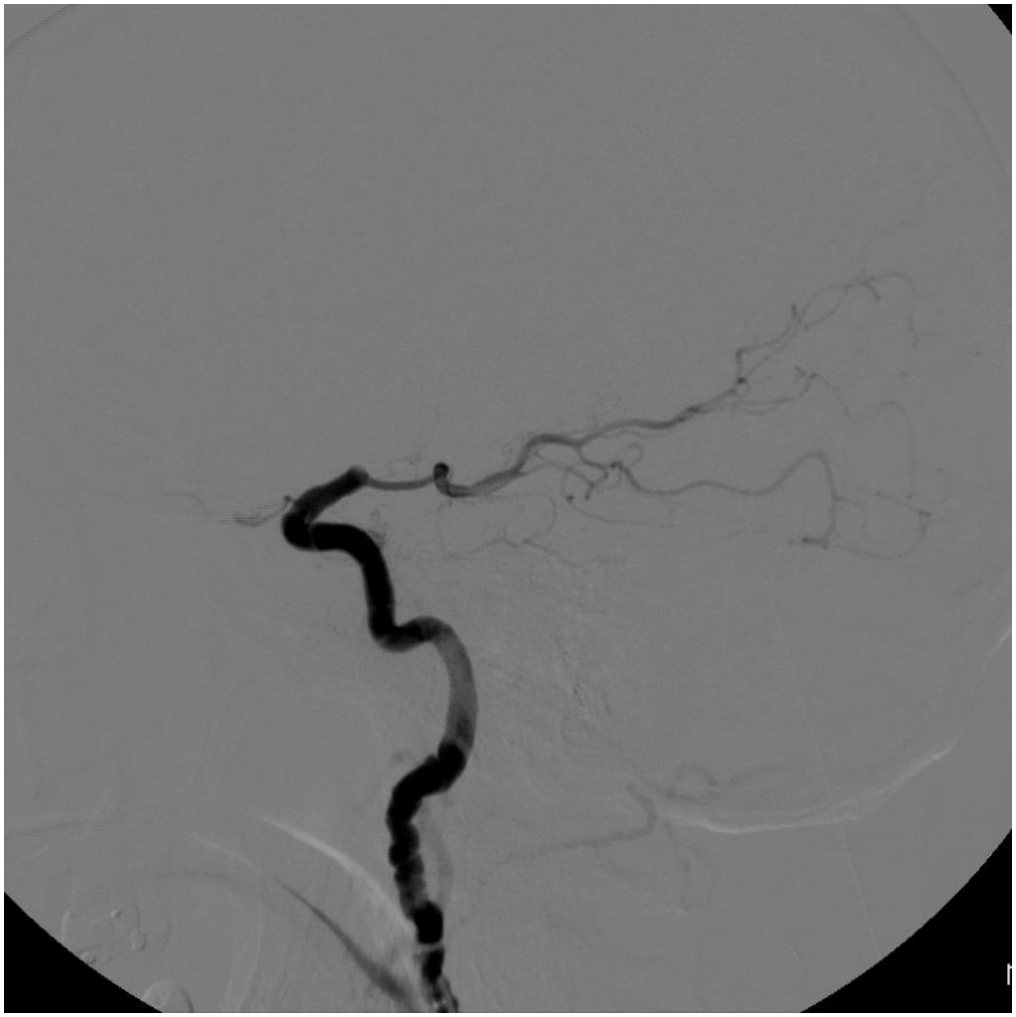
- Arrival at EVT center 13 hours after stroke onset

What would you do?

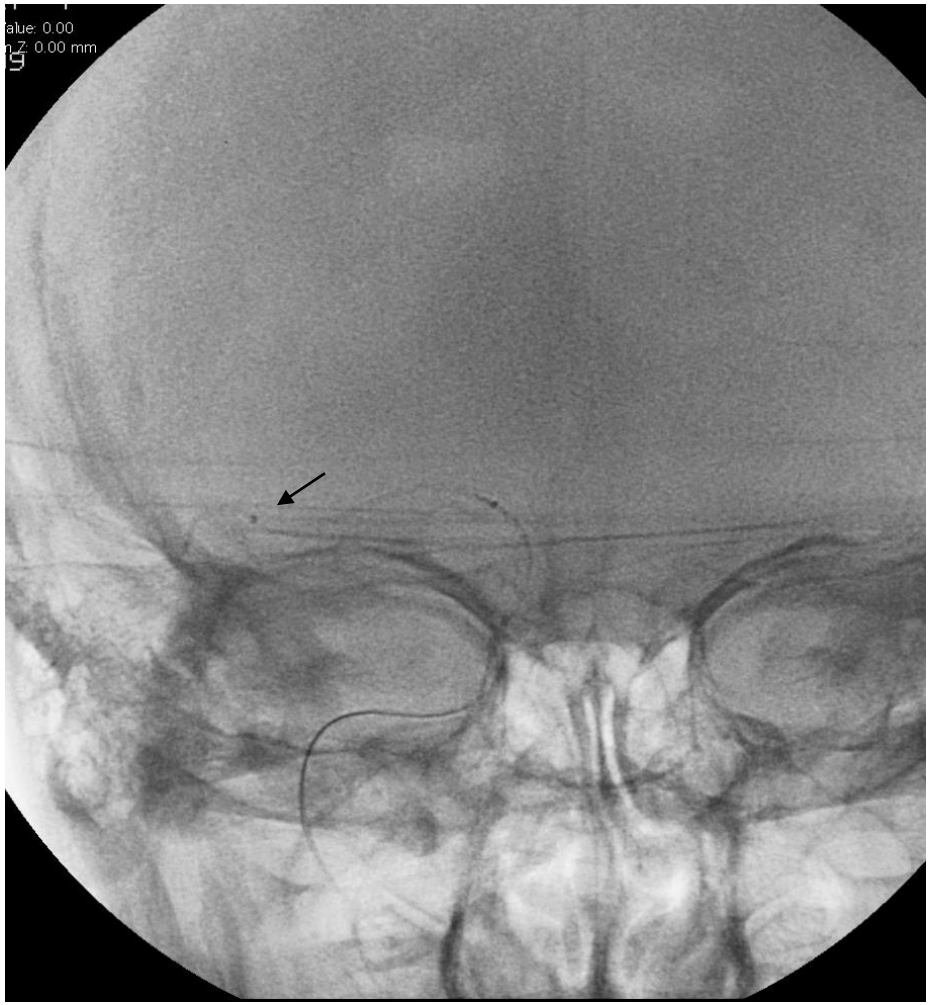
Mechanical Thrombectomy

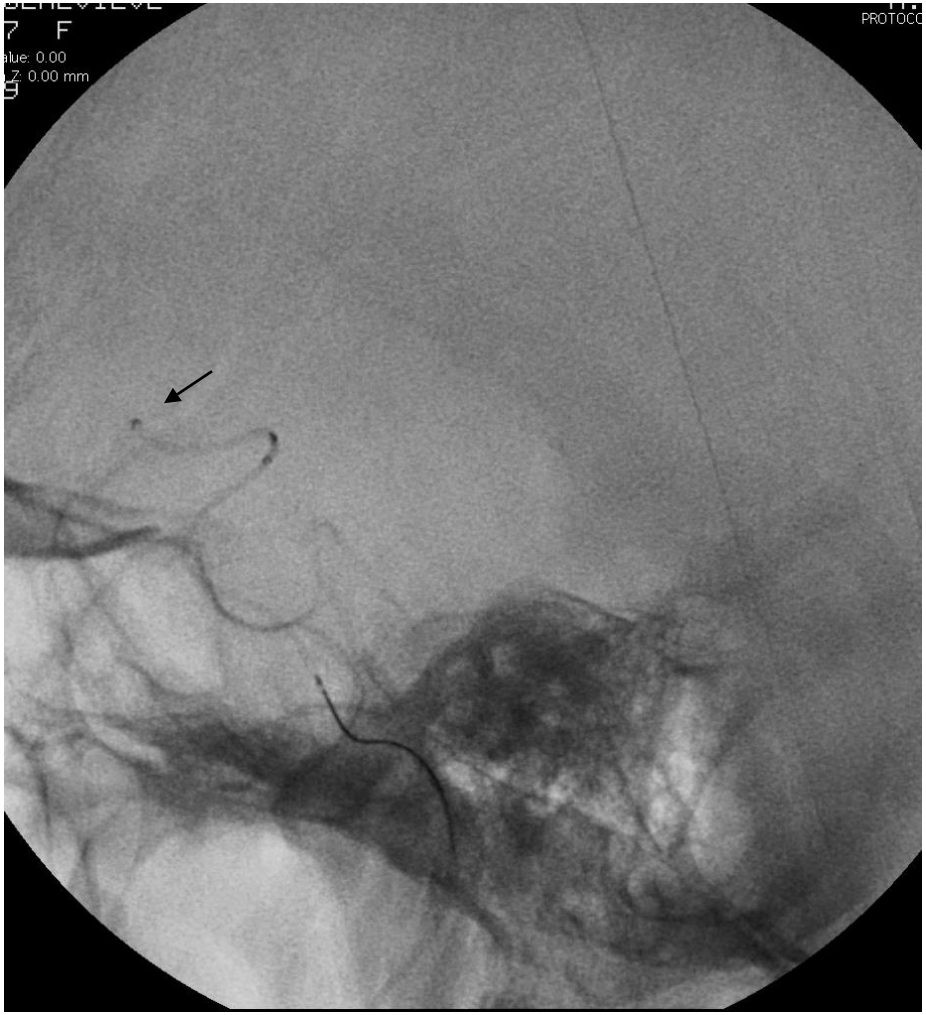
Initial Angiogram



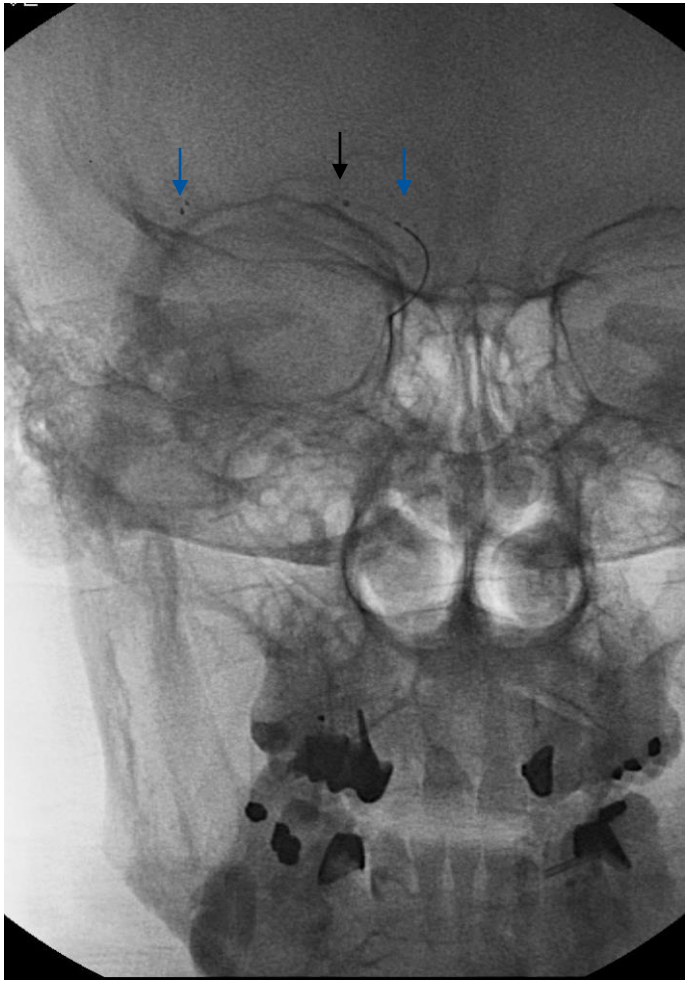


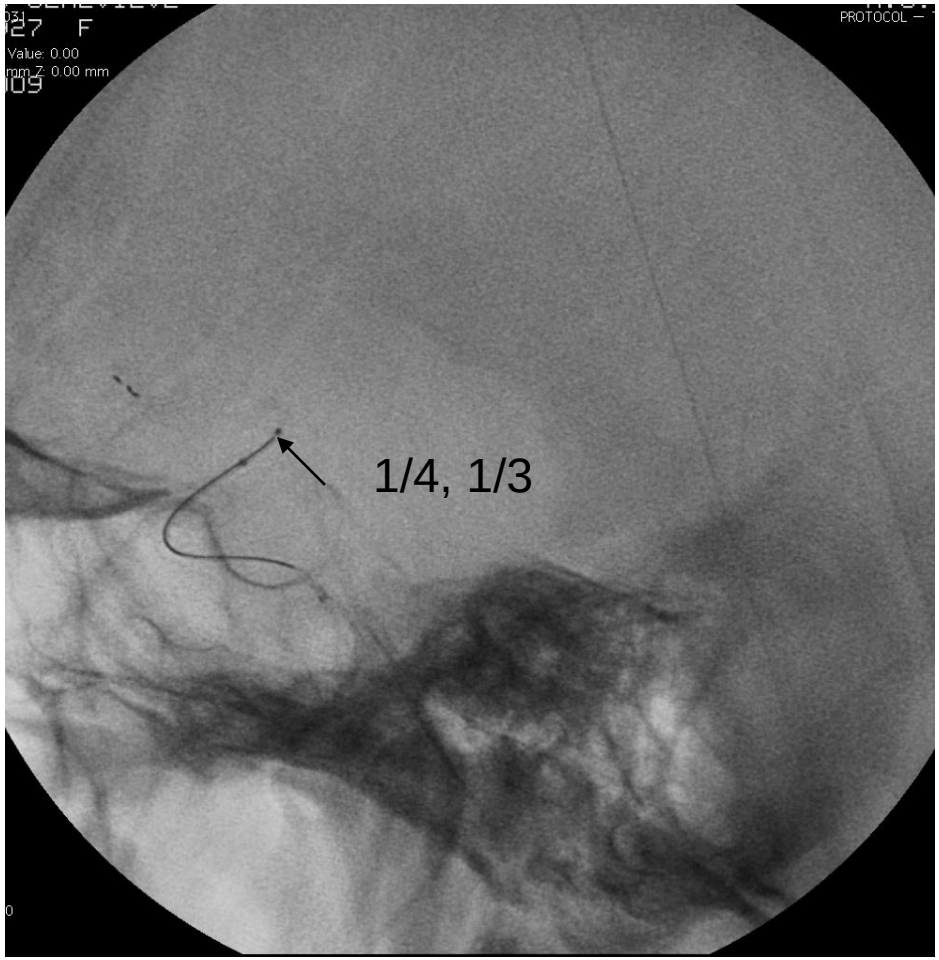
Microcatheter positioning





Mechanical Thrombectomy





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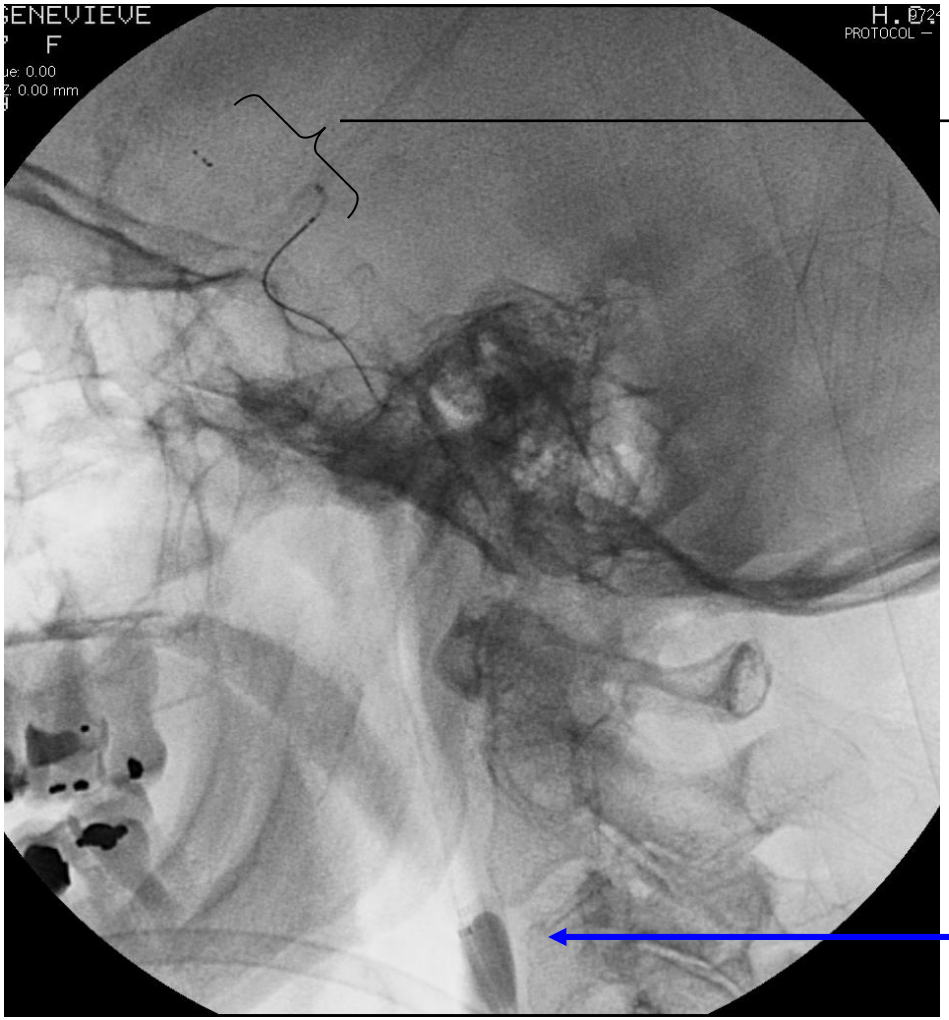

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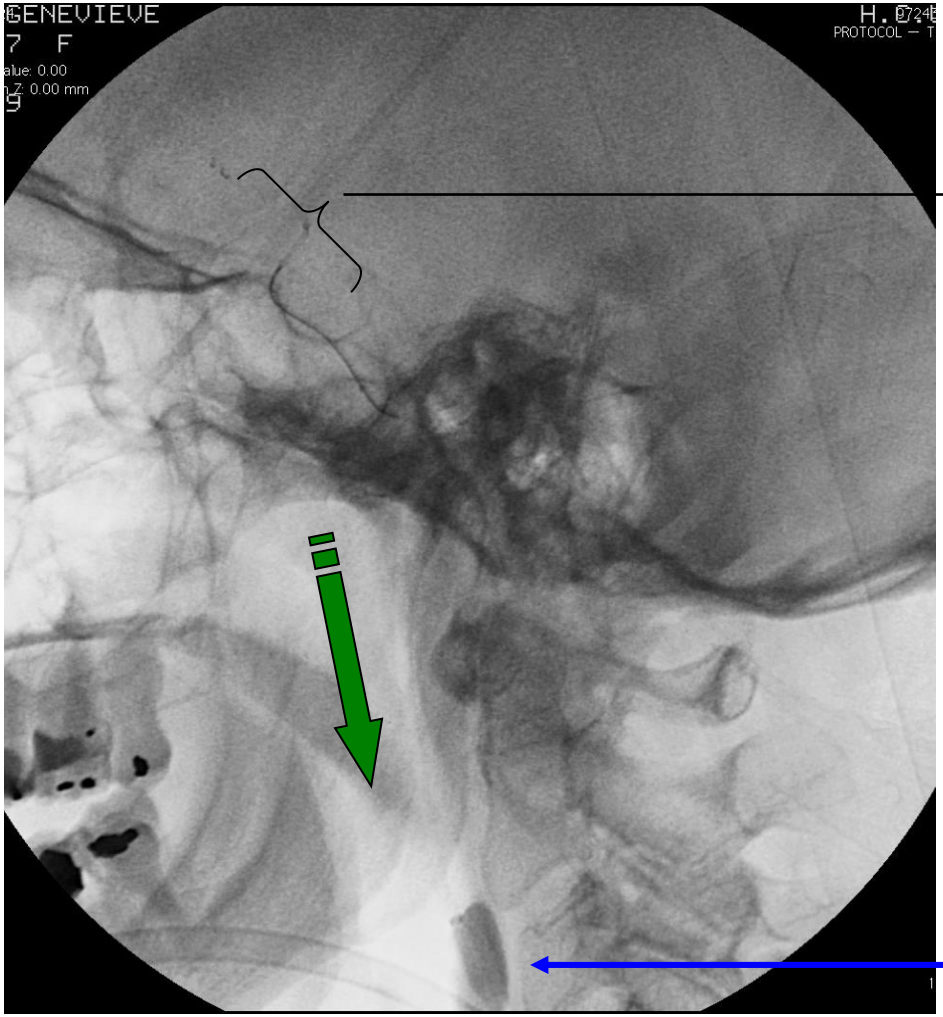
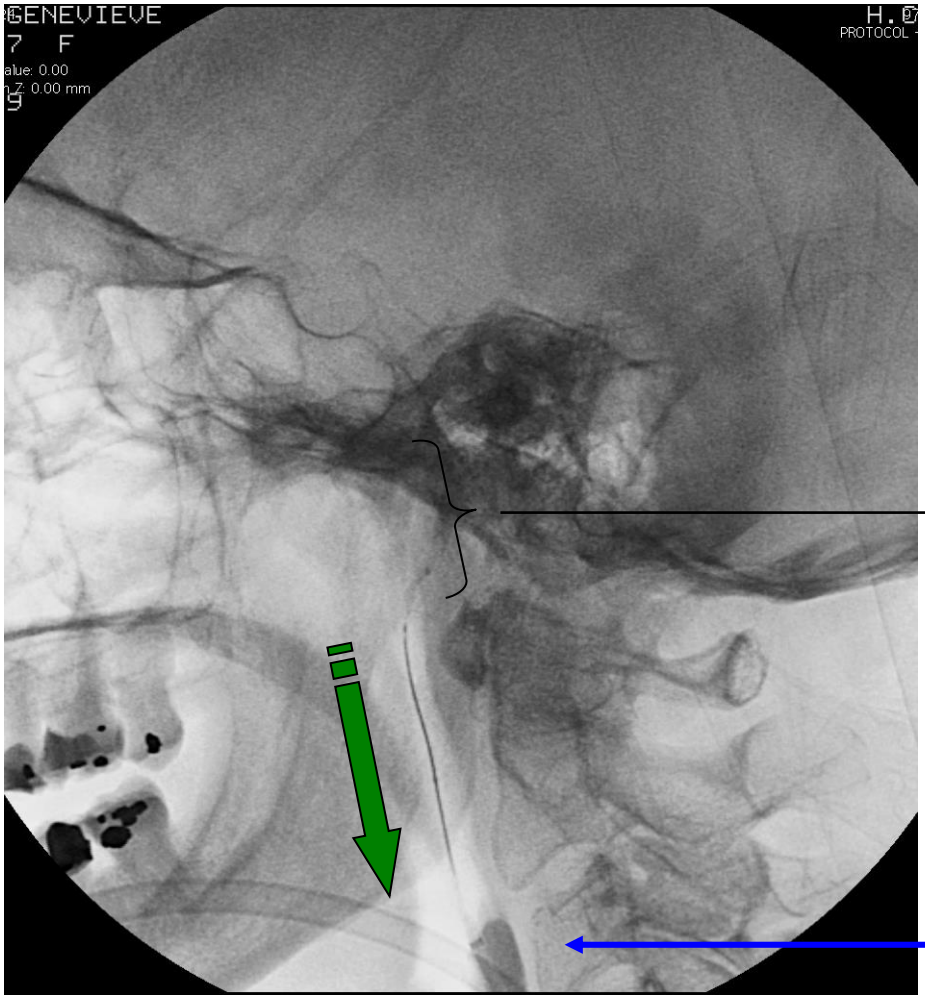


Solitaire device

Guiding Balloon inflated

Mechanical Thrombectomy



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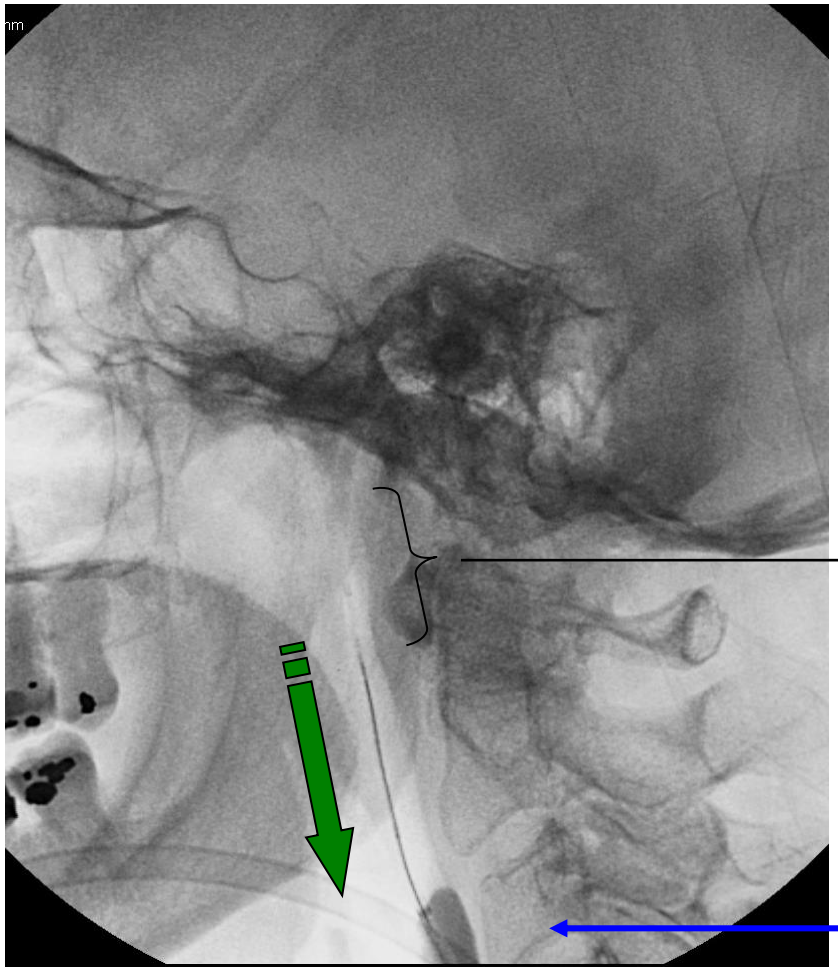

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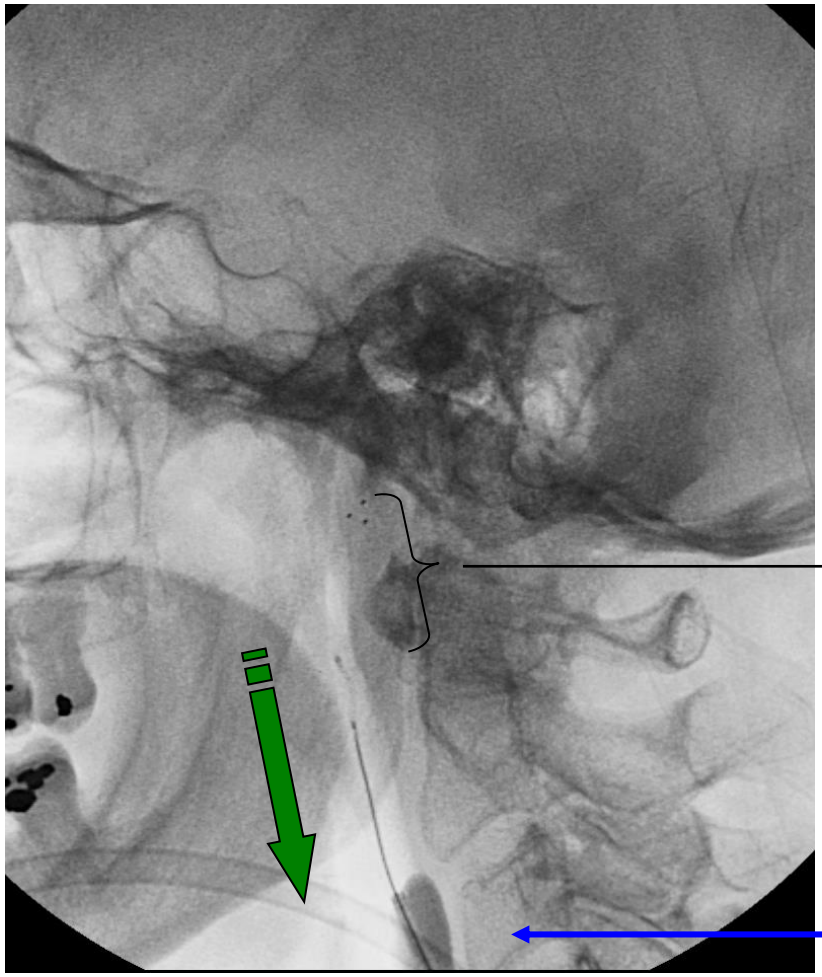

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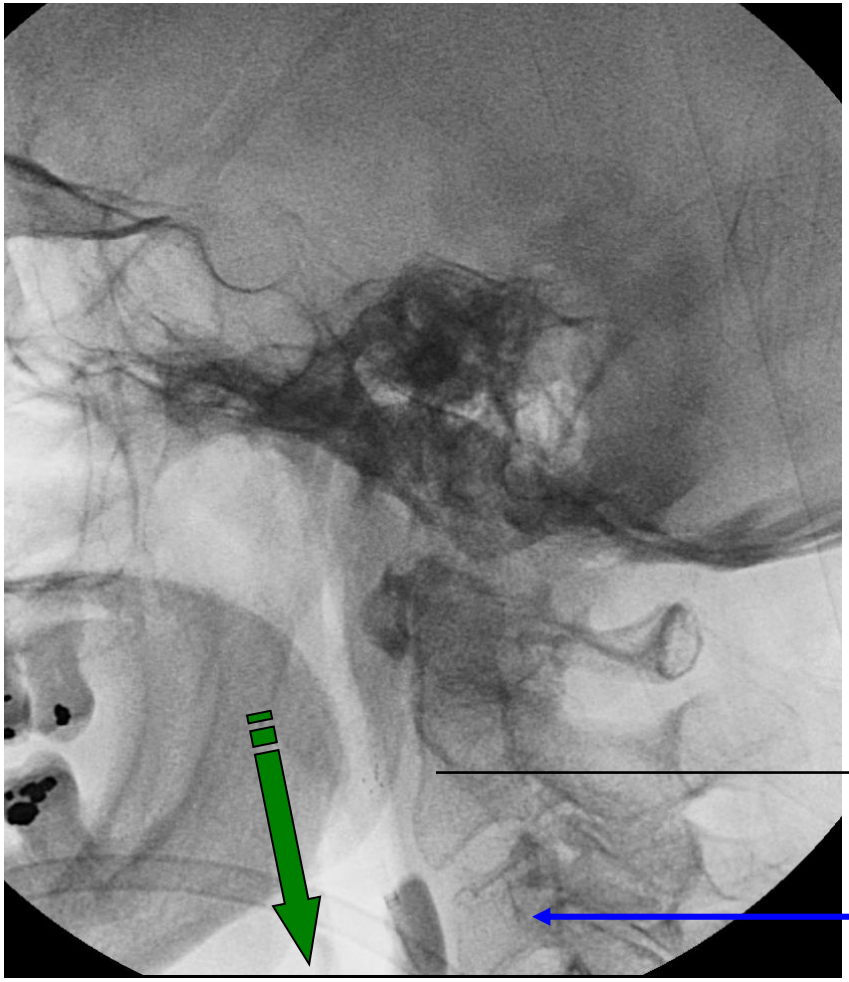
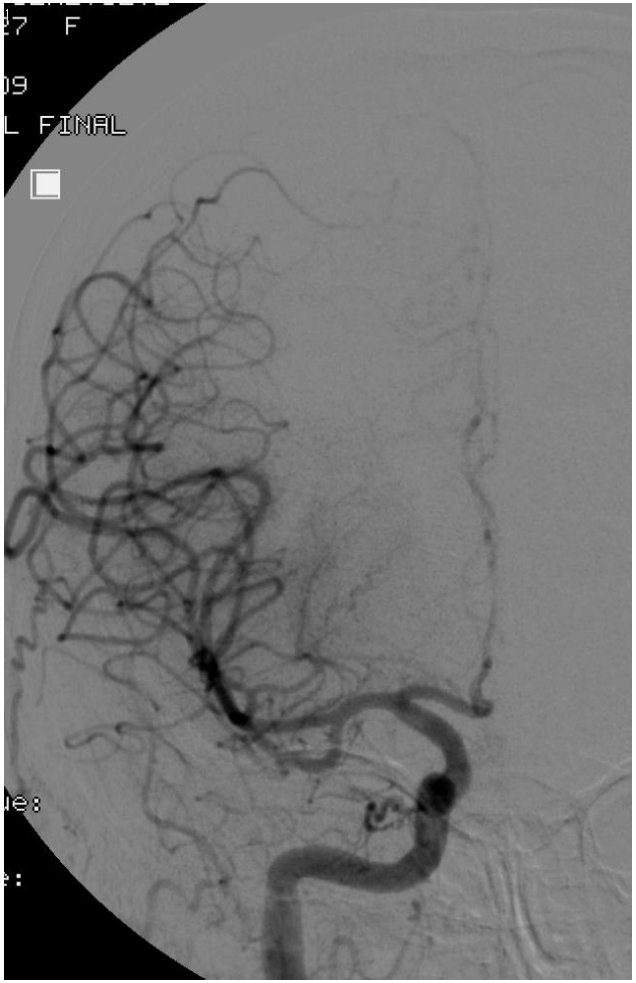
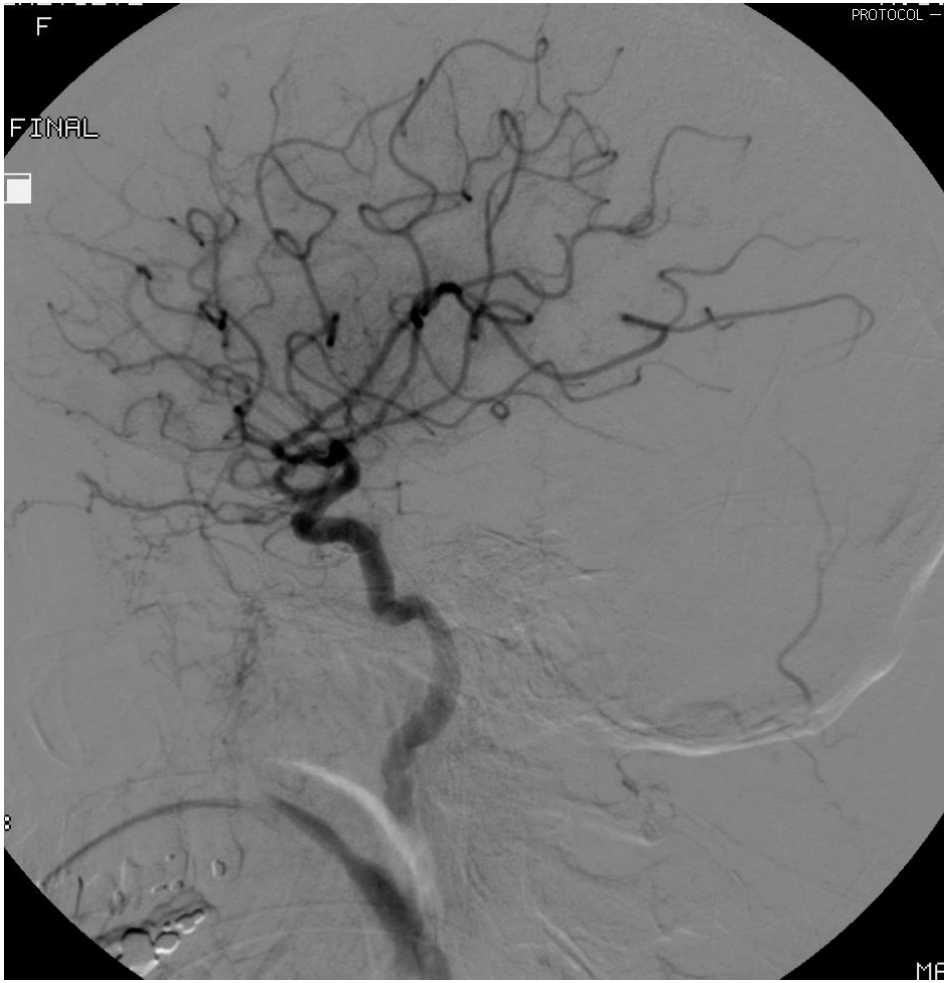
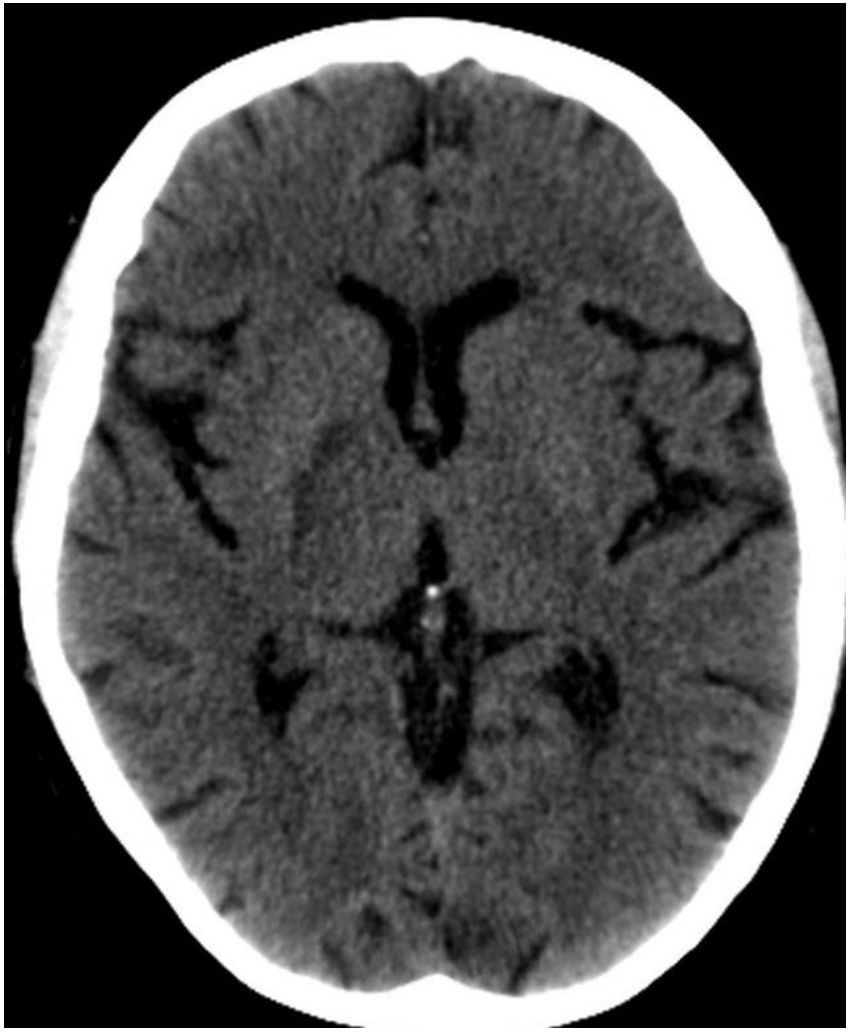


Final Angiography: Complete reperfusion





Follow-up imaging

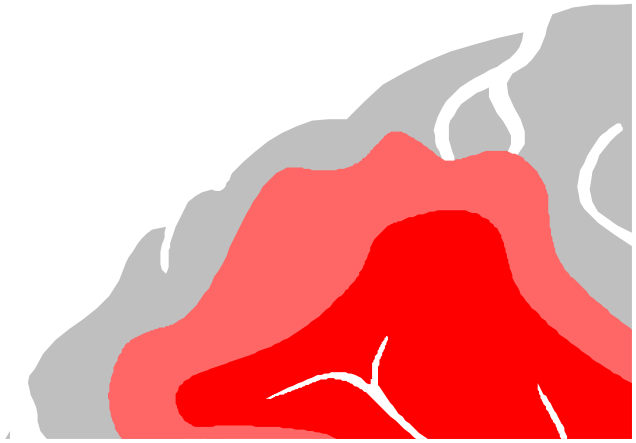


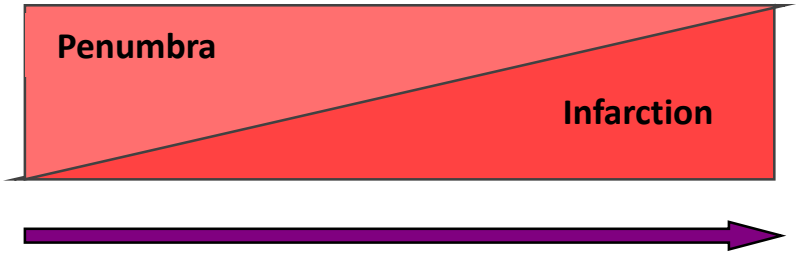
- Procedure time - 17min (1 operator)
- Conscious sedation
- NIHSS - 1 at 5 days
- mRS 0 at 90 days

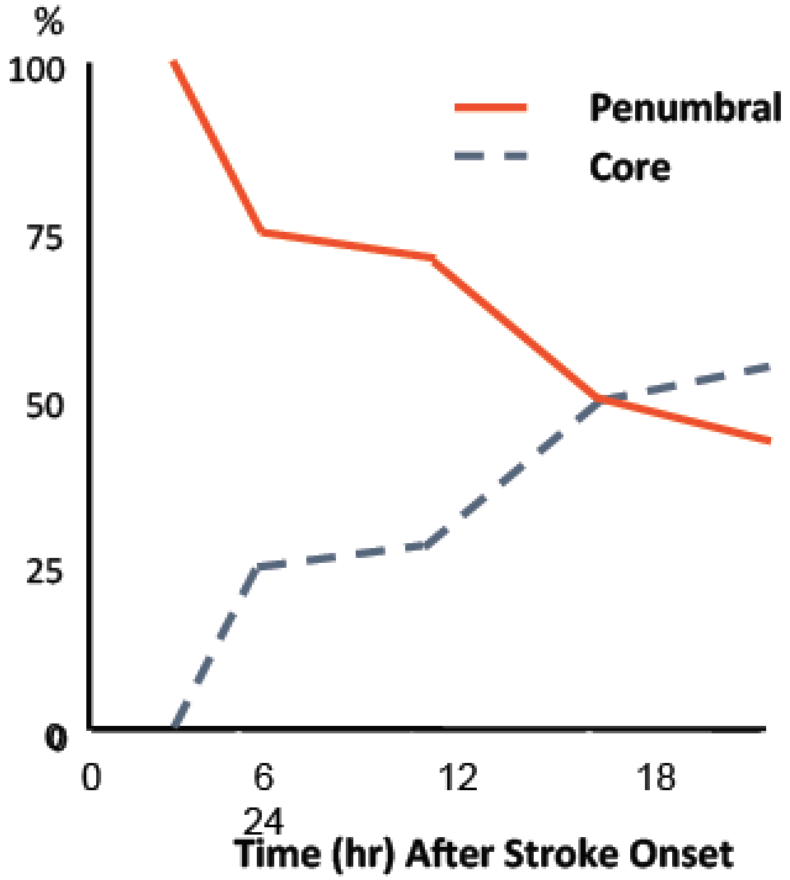
Late presenter paradox

- **How to explain apparent larger treatment benefits with later treatment?**

Ischemic Penumbra

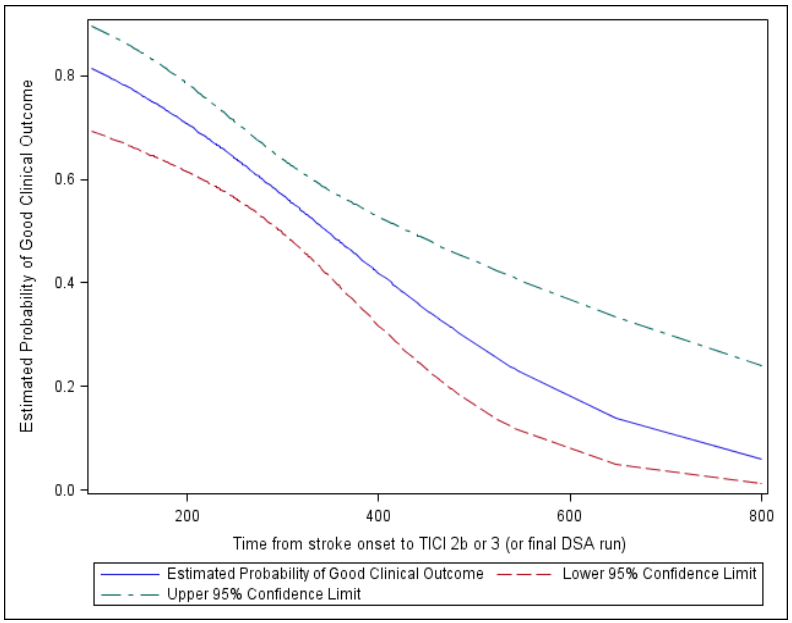




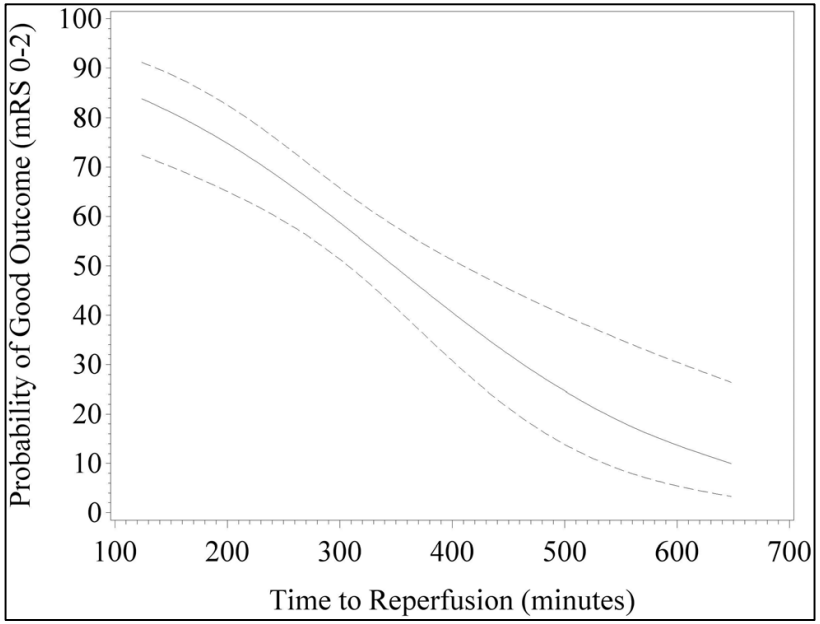


Time is an independent outcome predictor

STAR study



STAR/SWIFT study



Stroke 2014, Ann Neurol 2015

Late presenter paradox

- **How to explain apparent larger treatment benefits with later treatment?**
  - Strokes evolve, and it's mainly dependent on collaterals[1]

1: Albers et al, Late Window Paradox, Stroke. 2018;

Int J Stroke. 2015 July ; 10(5): 723–729. doi:10.1111/ijs.12436.

The Growth Rate of Early DWI Lesions is Highly Variable and Associated with Penumbral Salvage and Clinical Outcomes Following Endovascular Reperfusion

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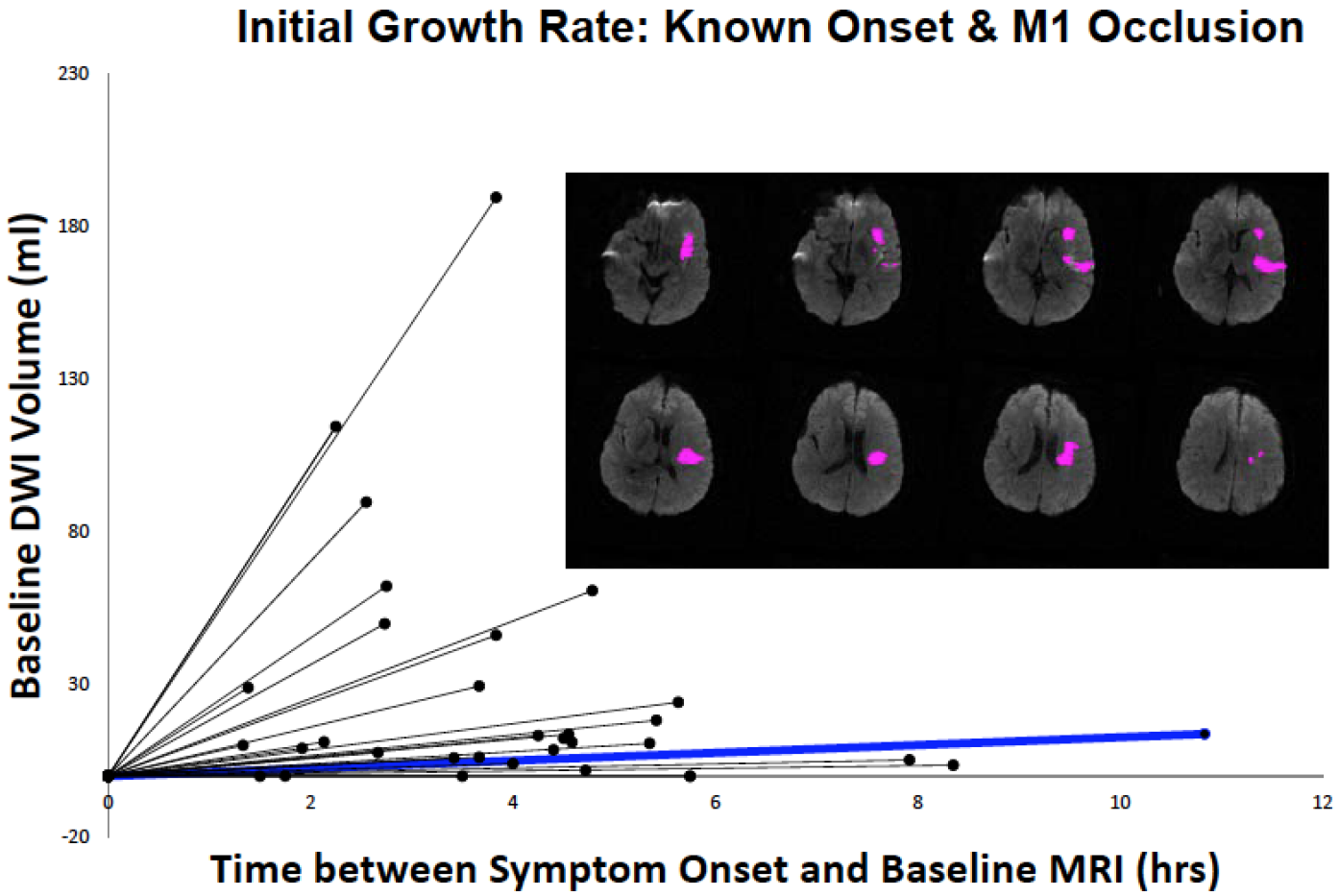

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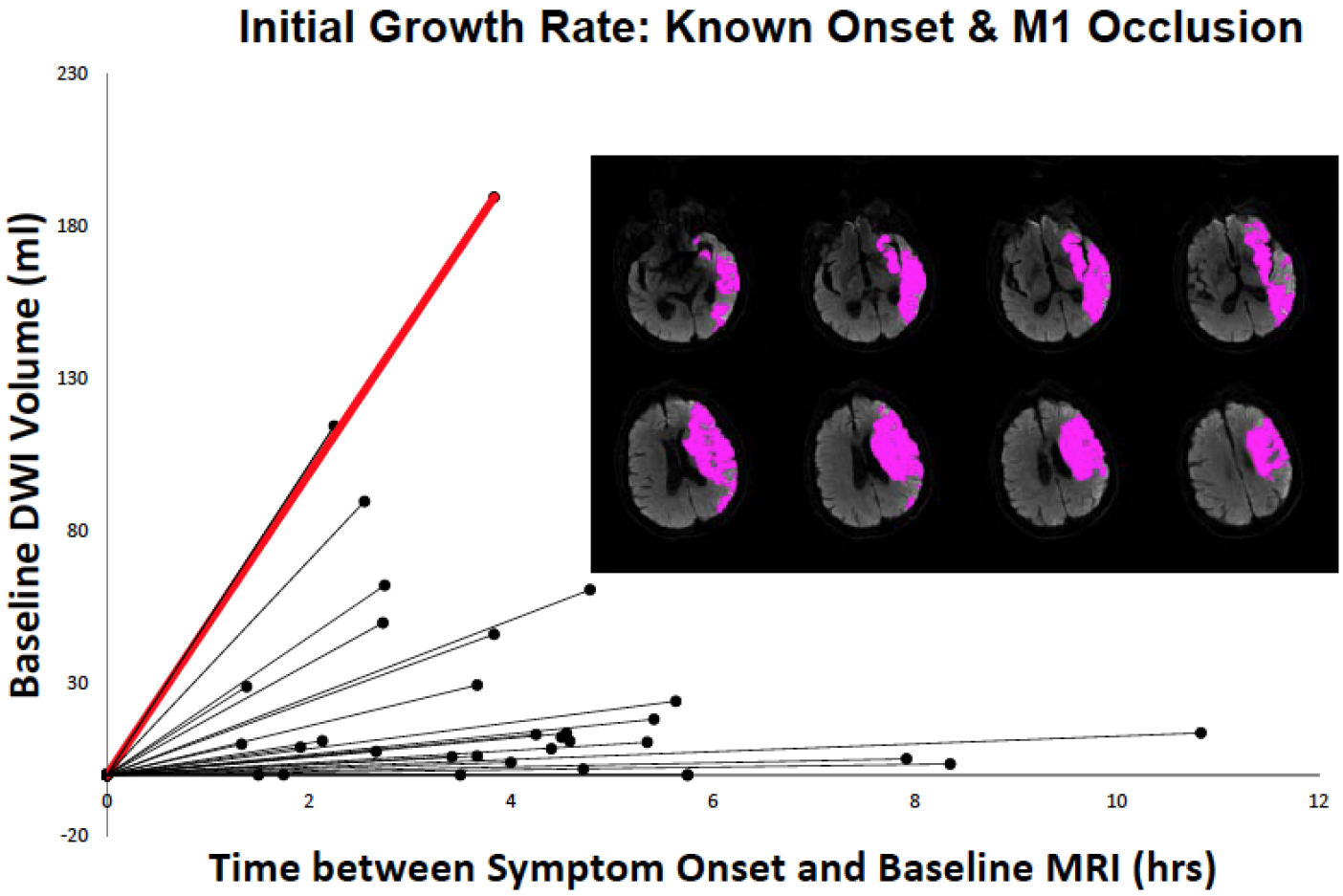

Int J Stroke. 2015 July ; 10(5): 723–729. doi:10.1111/ijs.12436.

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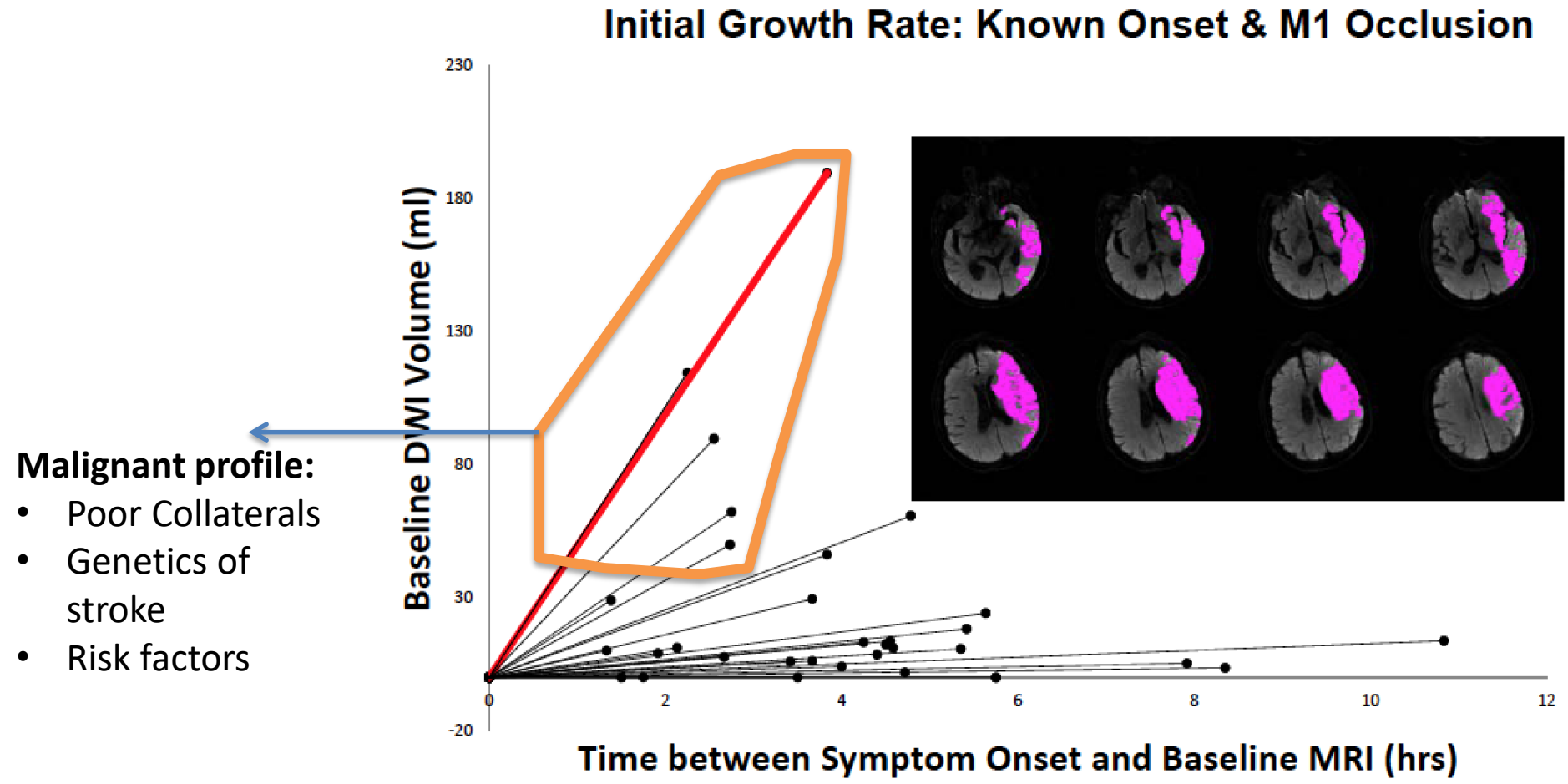


Malignant profile:

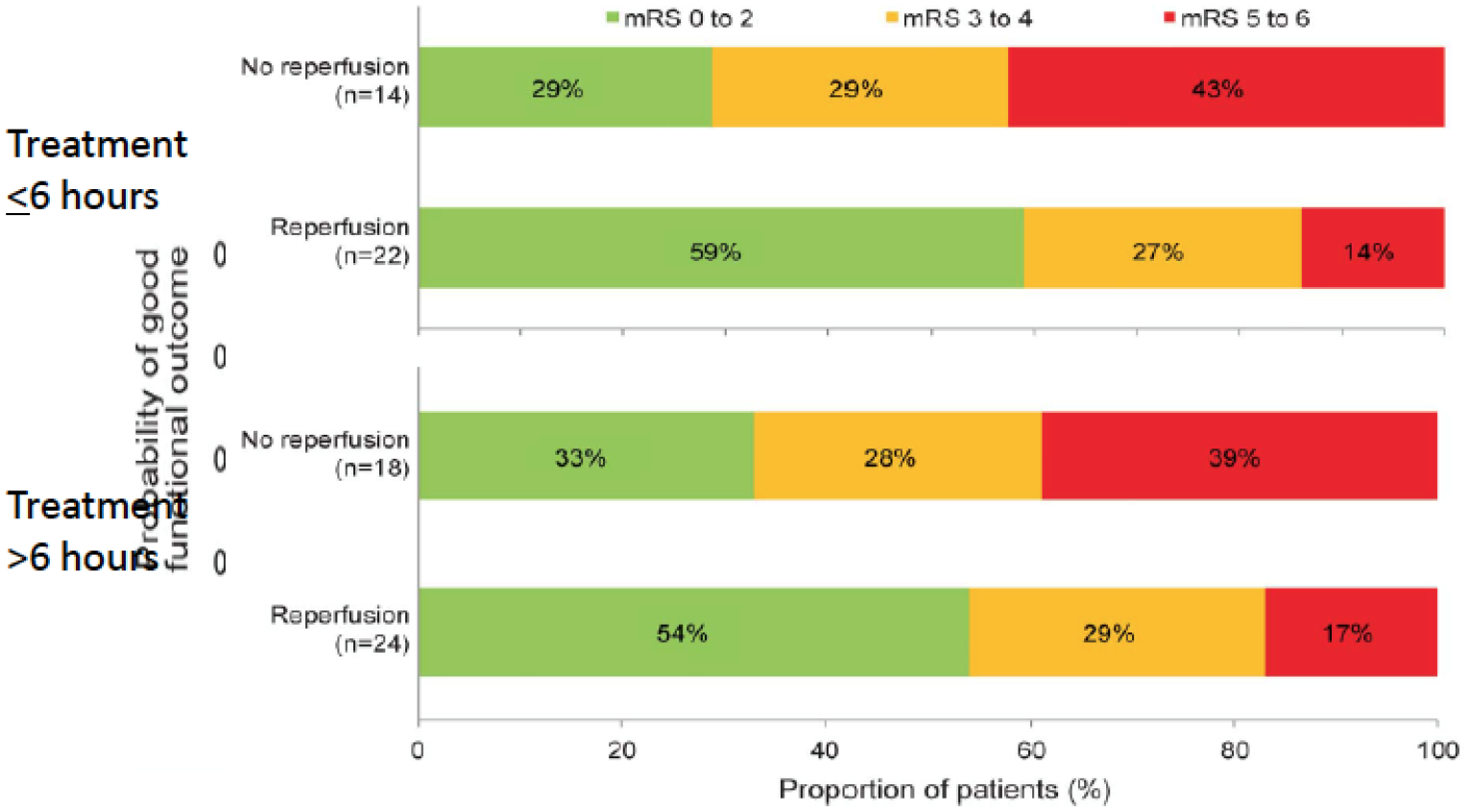
- Poor Collaterals
- Genetics of stroke
- Risk factors

Late presenter paradox

- **How to explain apparent larger treatment benefits with later treatment?**
  - Strokes evolve, and it's mainly dependent on collaterals[1]
    - DEFUSE 2 showed that it usually takes 3 days for max. infarct size in non-reperfused patients

1: Albers et al, Late Window Paradox, Stroke. 2018;

Time is an independent outcome predictor?



Response to reperfusion is not time dependent in patients with salvageable tissue

DEFUSE 2, Neurol 2015

Late presenter paradox

- **How to explain apparent larger treatment benefits with later treatment?**
  - Strokes evolve, and it's mainly dependent on collaterals[1]
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    - These collaterals will eventually fail and infarct volumes will eventually increase

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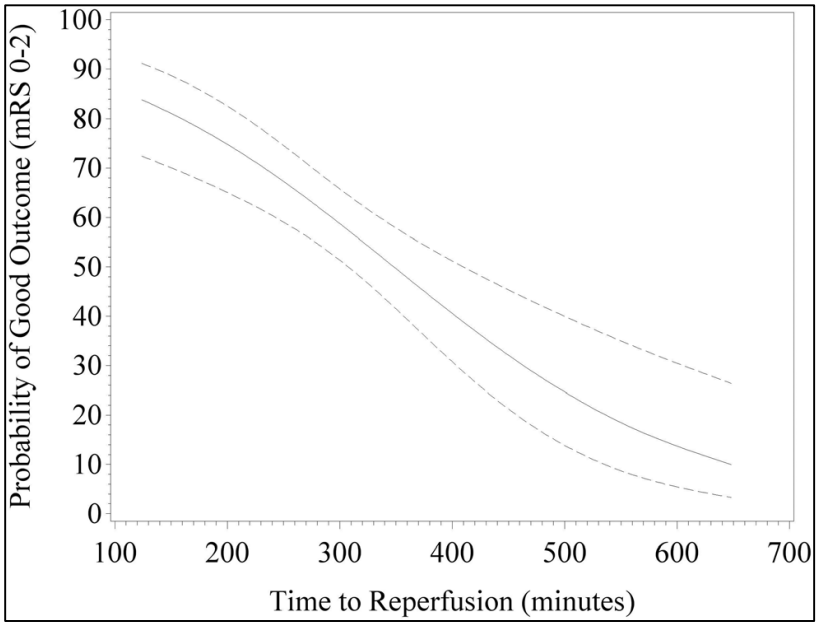
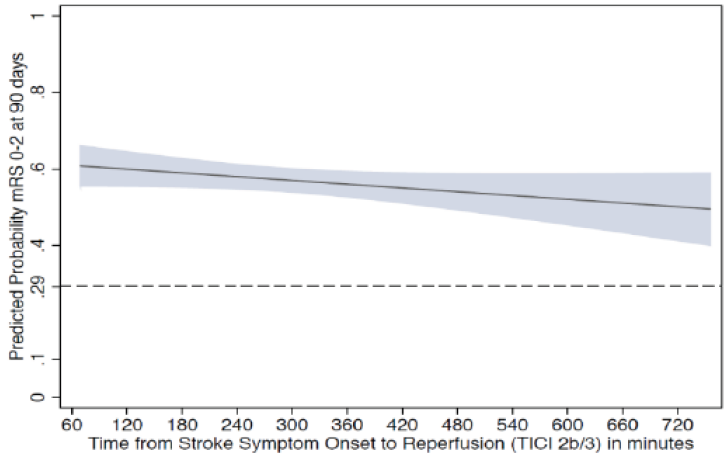
Time is an independent outcome predictor?

STAR/SWIFT study



ESCAPE

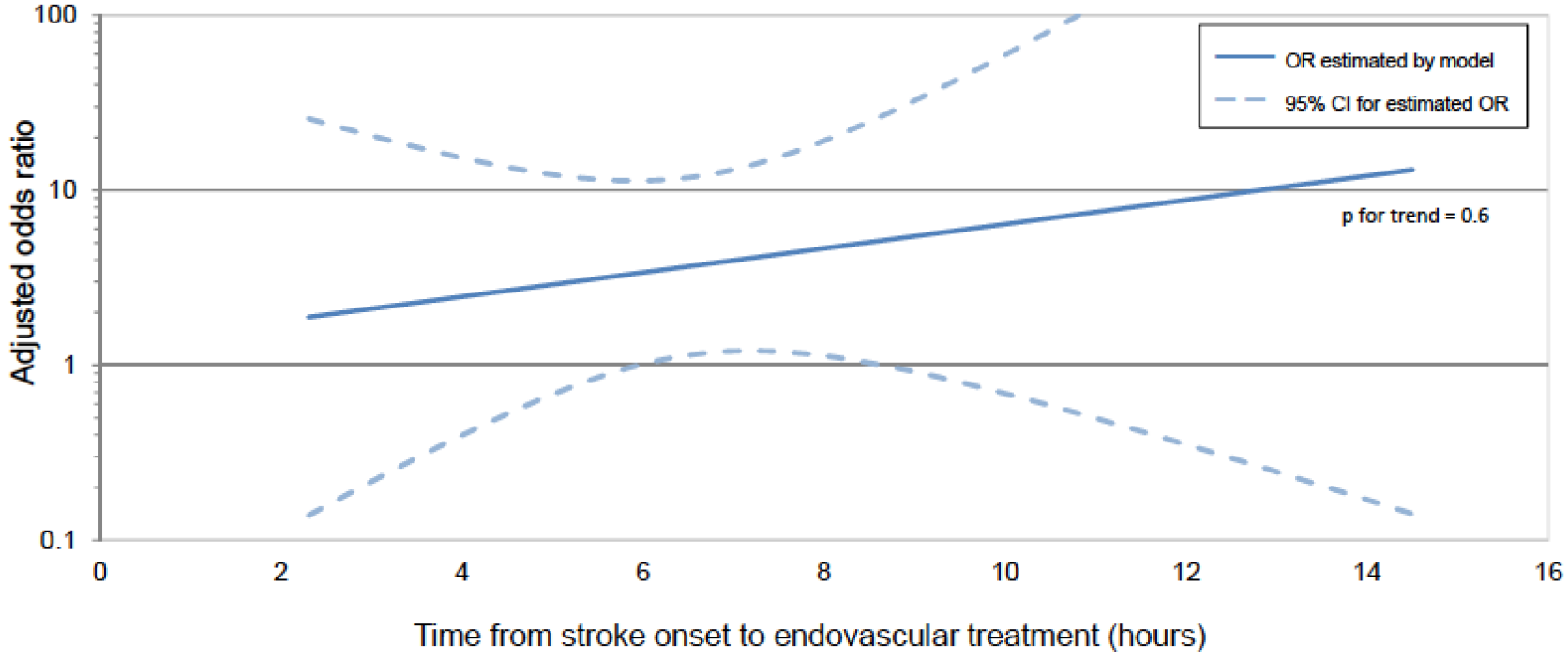


N=113
Median ASPECTS = 9

Early trials had low restrictions on core size
On inclusion

Stroke 2014, Ann Neurol 2015

Time is an independent outcome predictor?



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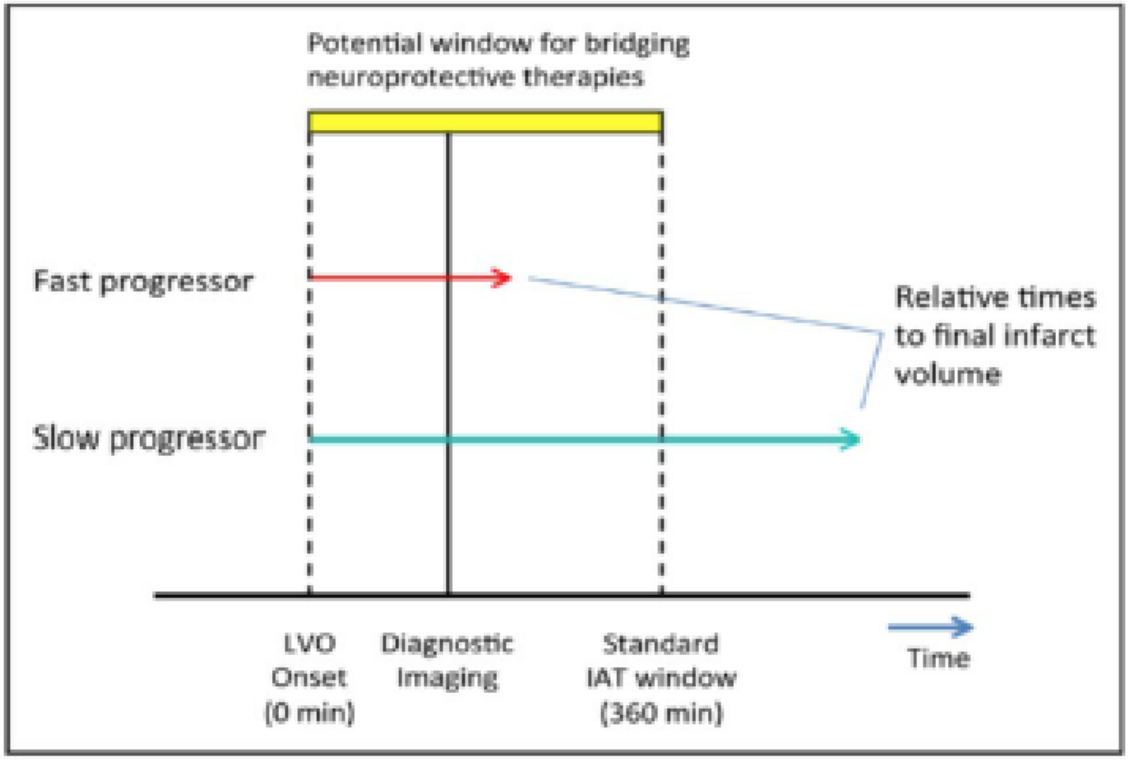
- **How to explain apparent larger treatment benefits with later treatment?**
  - Strokes evolve, and it's mainly dependent on collaterals[1]
    - DEFUSE 2 showed that it usually takes 3 days for max. infarct size in non-reperfused patients
    - These collaterals will eventually fail and infarct volumes will eventually increase
  - Fast x Slow Progressors!

1: Albers et al, Late Window Paradox, Stroke. 2018;

Fast Versus Slow Progressors of Infarct Growth in Large Vessel Occlusion Stroke

Clinical and Research Implications

Marcelo Rocha, MD, PhD; Tudor G. Jovin, MD



Late Therapeutic Window Trials

- DAWN
- DEFUSE 3

Late therapeutic window paradox?

Imaging-Based Endovascular Therapy for Acute Ischemic Stroke due to Proximal Intracranial Anterior Circulation Occlusion Treated Beyond 8 Hours From Time Last Seen Well

Retrospective Multicenter Analysis of 237 Consecutive Patients

Tudor G. Jovin, MD; David S. Liebeskind, MD; Rishi Gupta, MD; Marilyn Rymer, MD; Ansaar Rai, MD; Osama O. Zaidat, MD, MS; Alex Abou-Chebl, MD; Blaise Baxter, MD; Elad I. Levy, MD; Andrew Barreto, MD; Raul G. Nogueira, MD

Background and Purpose—Current selection criteria for intra-arterial therapies in the anterior circulation use time windows of 8 hours. Modern neuroimaging techniques have identified individuals with salvageable penumbra who present beyond this timeframe. We sought to assess safety, procedural, and clinical outcomes of MRI or CT perfusion imaging-based endovascular therapy in patients with anterior circulation stroke treated beyond 8 hours from time last seen well.

Methods—We conducted a multicenter retrospective review of consecutive patients meeting the following criteria: (1) acute proximal intracranial anterior circulation occlusion; (2) endovascular treatment initiated >8 hours from time last seen well; and (3) treatment selection based on MRI or CT perfusion imaging.

Results—Two hundred thirty-seven patients were identified (mean age, 63.8±16 years; mean baseline National Institutes of Health Stroke Scale, 15±5.5; mean time last seen well to treatment, 15±11.2 hours; male gender, 46%). Successful revascularization was achieved in 175 of 237 (73.84%) patients. Parenchymal hematoma occurred in 21 of 237 (8.86%) patients. The 90-day mortality rate was 21.5% (51 of 237). The rate of good outcomes was 45% (100 of 223) in the 223 patients with available modified Rankin Scale data at 90 days or time of hospital discharge. In multivariate analyses, age (OR, 0.96; 95% CI, 0.94 to 0.98; $P=0.002$), admission National Institutes of Health Stroke Scale (OR, 0.93; 0.87 to 0.98; $P=0.016$), and successful revascularization (OR, 4.32; 1.99 to 9.39; $P<0.0001$) were identified as independent predictors of good outcomes.

Conclusions—Endovascular therapy can be instituted with acceptable safety beyond 8 hours from time last seen well when selection is based on advanced neuroimaging. Successful revascularization is significantly associated with higher rates of good outcomes. The benefit of this approach compared with standard medical therapy should be assessed in a prospective randomized trial. (***Stroke*. 2011;42:2206-2211.**)

DAWN trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

DAWN trial

Study organization

Study principal investigators

Tudor G. Jovin, MD

Raul Nogueira, MD

Steering committee

Blaise Baxter, MD

Prof. Alain Bonafe

Anthony Furlan, MD

Rishi Gupta, MD

Prof. Olav Jansen

Demetrius Lopes, MD

Vitor Pereira, MD

Marc Ribo, MD

Jeffrey Saver, MD

Core lab

Neurovascular Research Imaging Core

David Liebeskind, MD

stryker

DAWN™ TRIAL

Data Safety Monitoring Board

Wade Smith, MD - chair

Daryl Gress, MD

Steven Hetts, MD

Roger Lewis, MD, PhD

Clinical Events Committee (CEC)

Timothy Malisch, MD

Ansaar Rai, MD

Kevin Sheth, MD

Independent Statisticians

Berry Consultants

Scott Berry PhD

Todd Graves PhD

DAWN TRIAL

DAWN trial

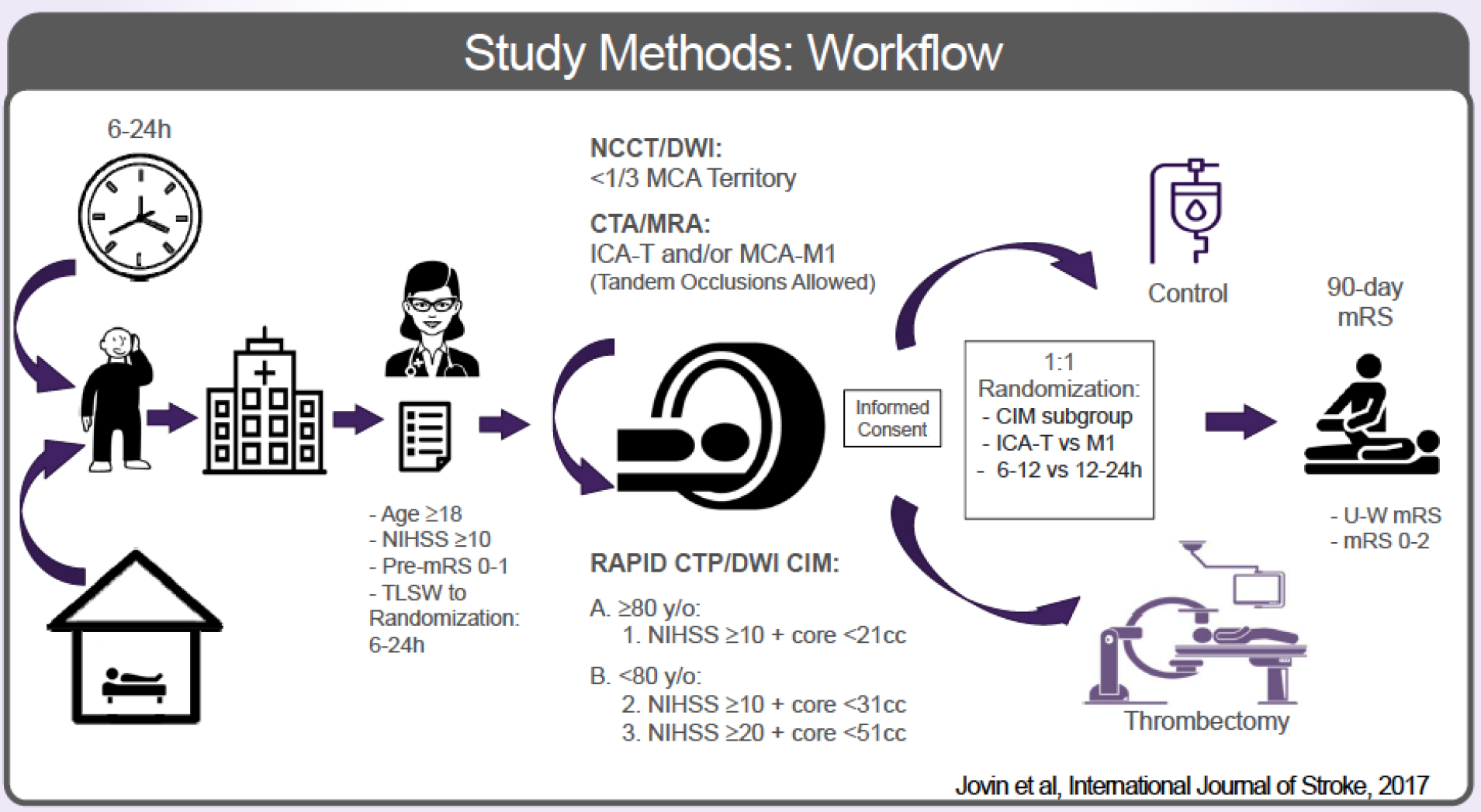
Study Design

Study design	Global, multi-center, adaptive, population enrichment, prospective, randomized, open, blinded endpoint (PROBE), controlled **FDA** IDE trial
Patient population	• Acute ischemic stroke (AIS) with large vessel occlusion • Able to be randomized between six to 24 hours after time last known well • Clinical imaging mismatch (CIM) defined by age, core, and NIHSS
Target vessel	Intracranial ICA, M1 segment of the MCA
Randomization	1:1 Trevo + medical management vs. medical management alone
Sites	Up to 50 sites worldwide (30 US and 20 international)
Sample size	500 maximum subjects: 250 in the treatment arm and 250 in the control arm. Minimum sample size is 150 subjects.
Follow-up	24 hours (-6/+24), day 5-7/discharge, day 30 (± 14), and day 90 (± 14)

TRIAL

Jovin et al. International Journal of Stroke. 2017

DAWN trial


Study Methods: Workflow
6-24h
NCCT/DWI:
<1/3 MCA Territory
CTA/MRA:
ICA-T and/or MCA-M1
(Tandem Occlusions Allowed)
Control
90-day
mRS
Informed
Consent
1:1
Randomization:
- CIM subgroup
- ICA-T vs M1
- 6-12 vs 12-24h
- Age ≥18
- NIHSS ≥10
- Pre-mRS 0-1
- TLSW to
Randomization:
6-24h
- U-W mRS
- mRS 0-2
RAPID CTP/DWI CIM:
A. ≥80 y/o:
1. NIHSS ≥10 + core <21cc
B. <80 y/o:
2. NIHSS ≥10 + core <31cc
3. NIHSS ≥20 + core <51cc
Thrombectomy
Jovin et al, International Journal of Stroke, 2017

DAWN trial

Study endpoints

Primary endpoint	**90-day disability assessed by the modified Rankin scale (mRS)** • Assessed via **Utility-Weighted mRS** • Nested **Dichotomous mRS 0-2**
Secondary endpoints	• "Early response" at day 5-7/discharge, defined as a NIHSS drop of ≥10 points from baseline or NIHSS score 0 or 1 • All cause mortality rates • Median final infarct size at 24 (-6/+24) hours from randomization • Revascularization rates at 24 (-6/+24) hours from randomization • Treatment arm: reperfusion rates post device and post procedure by angiography core lab measurement of modified TICI > 2b
Primary safety endpoint	**Stroke related mortality at 90 days**
Secondary safety endpoint	• Incidence of SICH, by ECASS III definition, within 24 (-6/+24) hours post randomization • Incidence of neurological deterioration from baseline NIHSS score through day 5-7/discharge • Incidence of procedure-related and device-related serious adverse events through 24 (-6/+24) hours post randomization

DAWN TRIAL

Jovin et al, International Journal of Stroke, 2017

Trial Design

- 26 centres worldwide
- At least 40 thrombectomy procedures per centre per year
- Trevo device

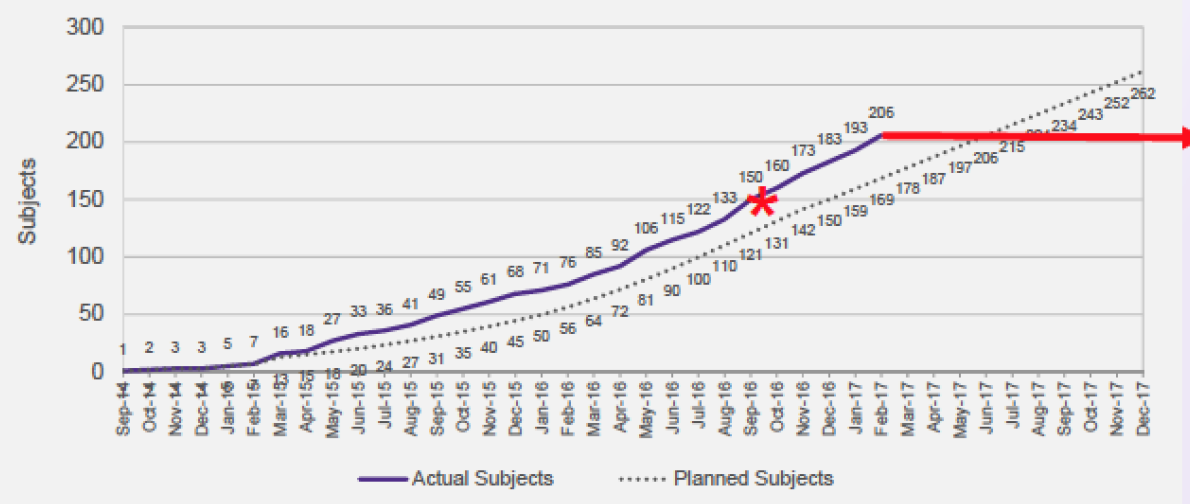
- Stenting of ICA not permitted
- Angioplasty of ICA was permitted

DAWN trial

TRIAL ENROLLMENT RATE AND TERMINATION

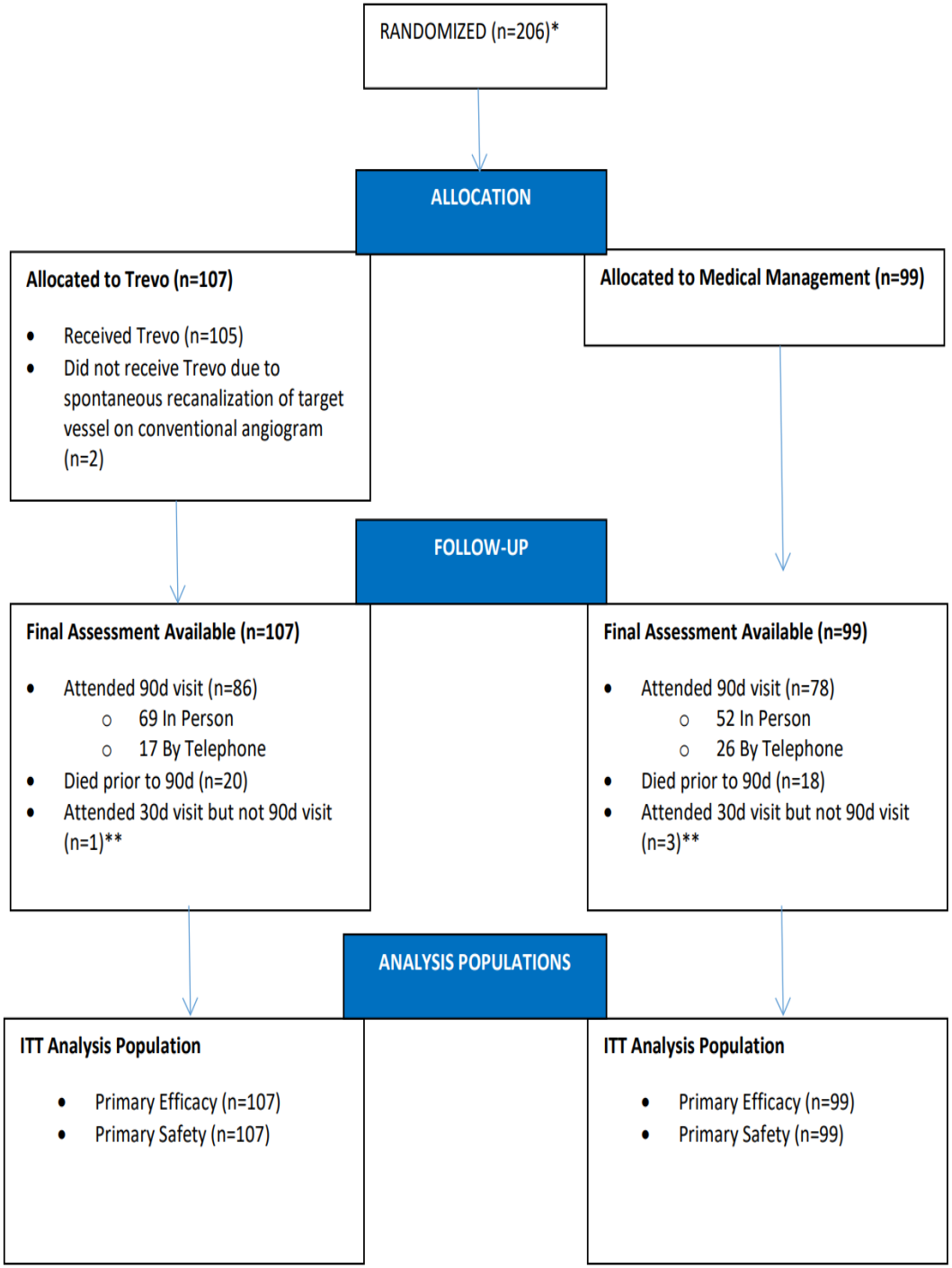
Site Status			
Sites Qualified	36	Contracts Executed	31
Sites Initiated	30	Sites Activated to Enroll	30
IRB/EC Approvals	31	Subjects Enrolled	206

Actual / Projected Enrollment



Enrollment stopped at DSMB recommendation.

*Boundary for first enrichment not crossed.


RANDOMIZED (n=206)*
ALLOCATION
Allocated to Trevo (n=107)
Received Trevo (n=105)
Did not receive Trevo due to spontaneous recanalization of target vessel on conventional angiogram (n=2)
Allocated to Medical Management (n=99)
FOLLOW-UP
Final Assessment Available (n=107)
Attended 90d visit (n=86)
69 In Person
17 By Telephone
Died prior to 90d (n=20)
Attended 30d visit but not 90d visit (n=1)**
Final Assessment Available (n=99)
Attended 90d visit (n=78)
52 In Person
26 By Telephone
Died prior to 90d (n=18)
Attended 30d visit but not 90d visit (n=3)**
ANALYSIS POPULATIONS
ITT Analysis Population
Primary Efficacy (n=107)
Primary Safety (n=107)
ITT Analysis Population
Primary Efficacy (n=99)
Primary Safety (n=99)

Results

Table 1. Characteristics of the Patients at Baseline.*

Variable	Thrombectomy Group (N=107)	Control Group (N=99)
Age — yr	69.4±14.1	70.7±13.2
Age ≥80 yr — no. (%)	25 (23)	29 (29)
Male sex — no. (%)	42 (39)	51 (52)
Atrial fibrillation — no. (%)	43 (40)	24 (24)
Diabetes mellitus — no. (%)	26 (24)	31 (31)
Hypertension — no. (%)	83 (78)	75 (76)
Previous ischemic stroke or transient ischemic attack — no. (%)	12 (11)	11 (11)
NIHSS score†		
Median	17	17
Interquartile range	13–21	14–21
10 to 20 — no. (%)	78 (73)	72 (73)
Treatment with intravenous alteplase — no. (%)	5 (5)	13 (13)

Results

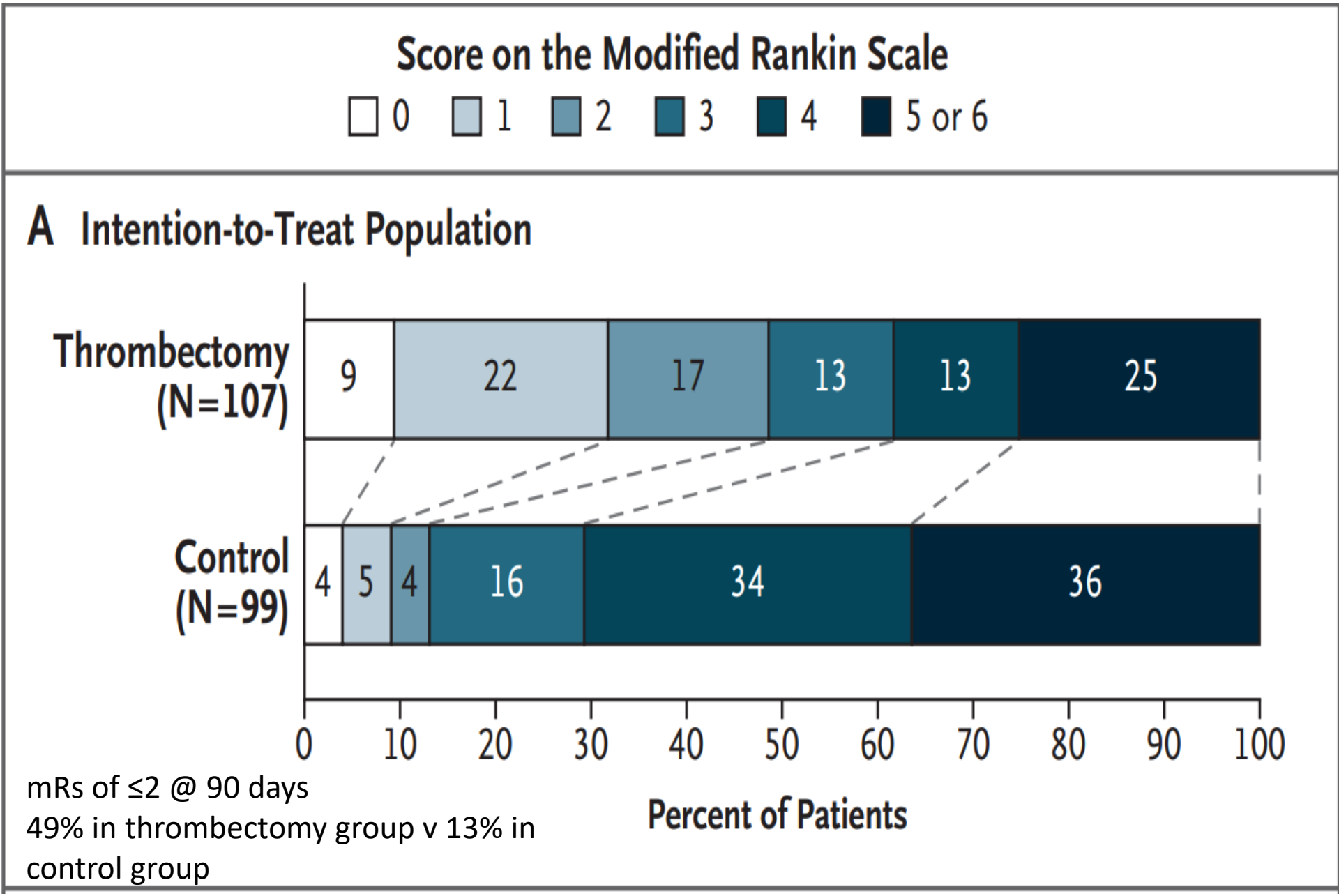
Infarct volume — ml		
Median	7.6	8.9
Interquartile range	2.0–18.0	3.0–18.1
Type of stroke onset — no. (%)‡		
On awakening	67 (63)	47 (47)
Unwitnessed stroke	29 (27)	38 (38)
Witnessed stroke	11 (10)	14 (14)
Occlusion site — no. (%)§		
Intracranial internal carotid artery	22 (21)	19 (19)
First segment of middle cerebral artery	83 (78)	77 (78)
Second segment of middle cerebral artery	2 (2)	3 (3)
Interval between time that patient was last known to be well and randomization — hr		
Median	12.2	13.3
Interquartile range	10.2–16.3	9.4–15.8
Range	6.1–23.5	6.5–23.9
Time from first observation of symptoms to randomization — hr		
Median	4.8	5.6
Interquartile range	3.6–6.2	3.6–7.8

Miscellanous

- Median baseline core by RAPID (IQR)
  - 7.6mls (2 – 18) thrombectomy group
  - 8.9mls (3 – 18) control group
- Time from qualifying imaging to arterial puncture: 57 min (36-84)
- Time from randomisation to arterial puncture: 16 min (9-29)
- Time LSW to revascularisation: 13.6 hours (11.3-18.0)

Table 2. Efficacy Outcomes.*

Outcome	Thrombectomy Group (N=107)	Control Group (N=99)	Absolute Difference (95% CI)†	Adjusted Difference (95% Credible Interval)‡	Posterior Probability of Superiority
Primary end points					
Score on utility-weighted modified Rankin scale at 90 days§	5.5±3.8	3.4±3.1	2.1 (1.2–3.1)	2.0 (1.1–3.0)	>0.999
Functional independence at 90 days — no. (%)¶	52 (49)	13 (13)	36 (24–47)	33 (21–44)	>0.999
				Risk Ratio (95% CI)	P Value
Secondary end points					
Early response — no. (%)‖	51 (48)	19 (19)	29 (16–41)	3 (2–4)	<0.001**
Recanalization at 24 hr — no. (%)††	82 (77)	39 (39)	40 (27–52)	2 (2–4)	<0.001**
Change from baseline in infarct volume at 24 hr — ml††					0.003‡‡
Median	1	13			
Interquartile range	0–28	0–42			
Infarct volume at 24 hour — ml††					<0.001‡‡
Median	8	22			
Interquartile range	0–48	8–68			
Grade of 2b or 3 on mTICI scale — no. (%)§§	90 (84)	NA			



mRs of ≤2 @ 90 days
49% in thrombectomy group v 13% in control group

DAWN trial

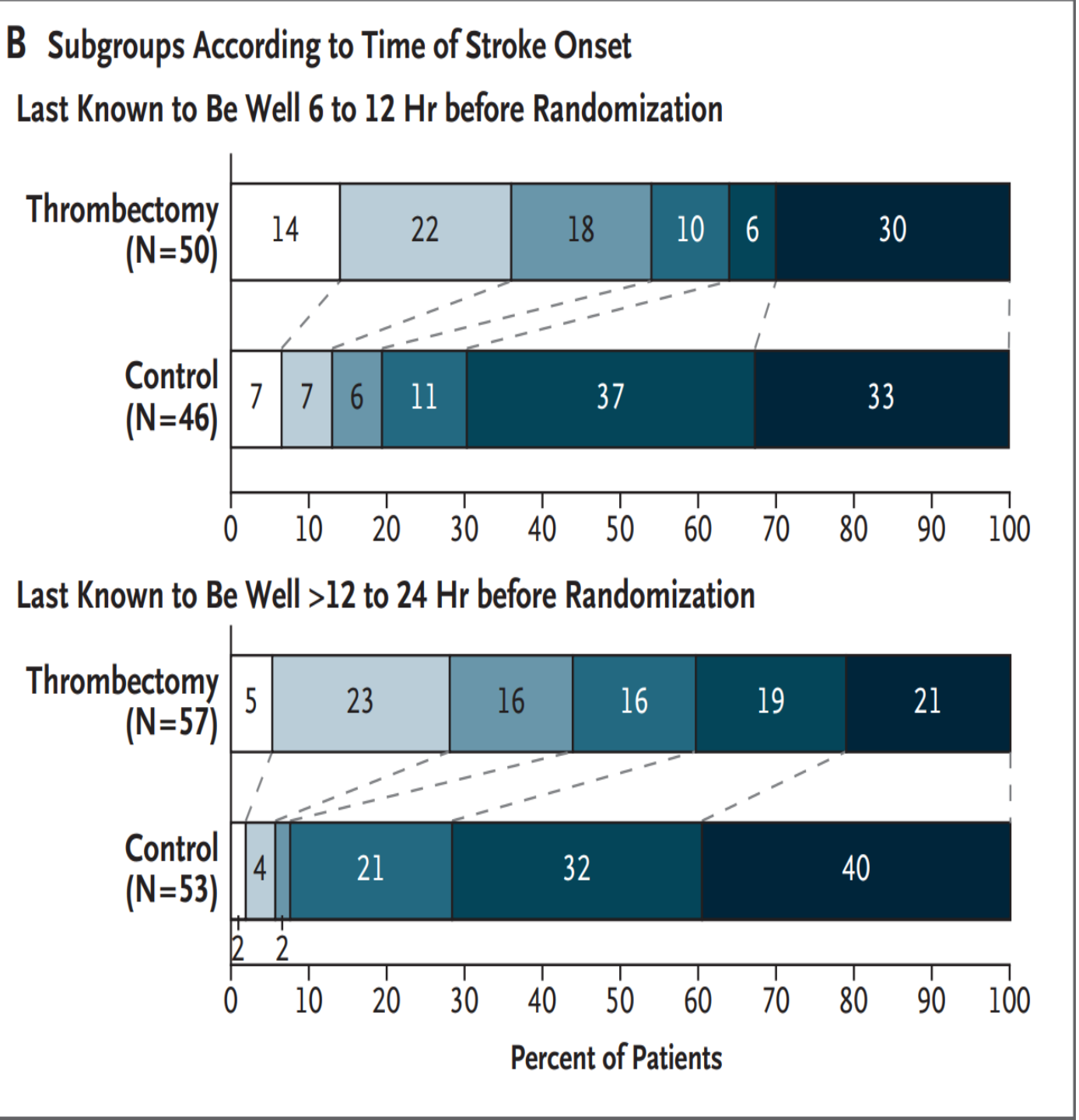
Procedural characteristics and outcomes

	Treatment arm N=107
Procedure duration (minutes) (median IQR)	56.0 [33.0-90.0]
Total number of Trevo device passes (median IQR)	2.0 [1.0-3.0]

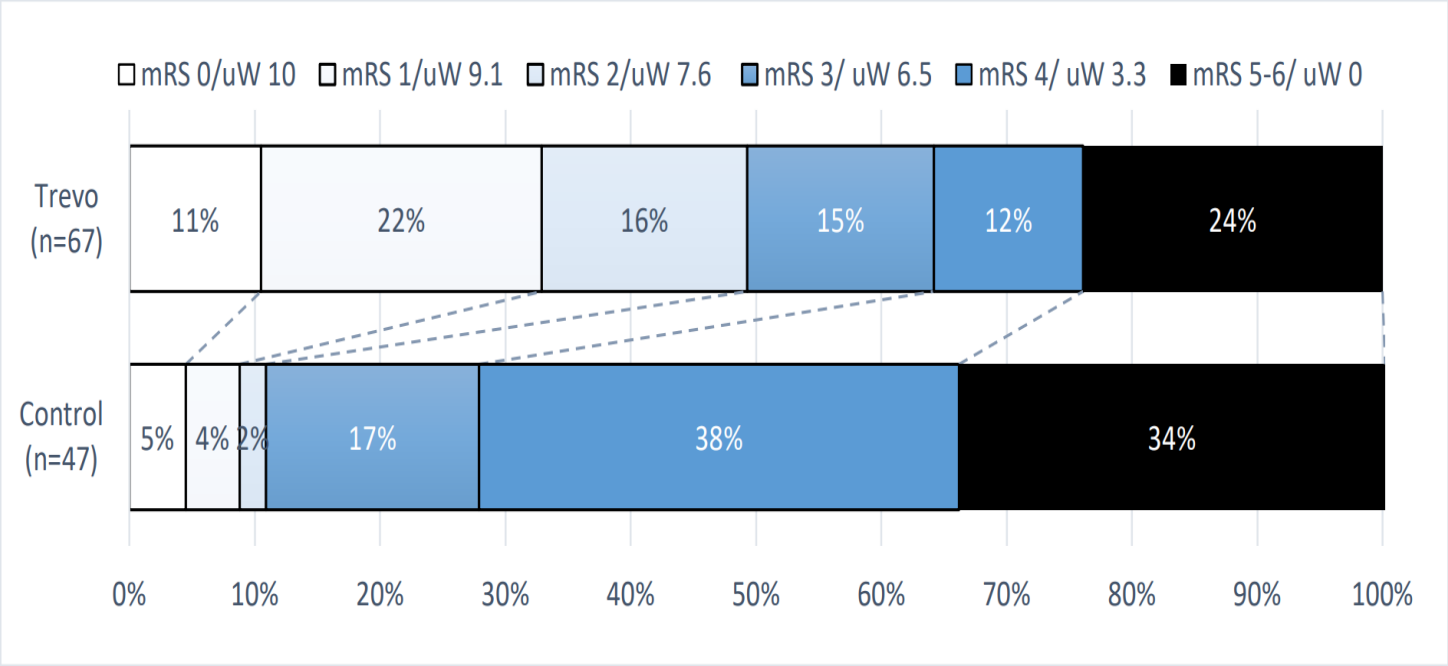
Core lab adjudicated TICIs	Treatment arm N=107
Post procedure mTICI ≥ 2B	84.0%
Post procedure oTICI ≥ 2B*	72.6%
Post procedure TICI 3	10.4%

DAWN TRIAL

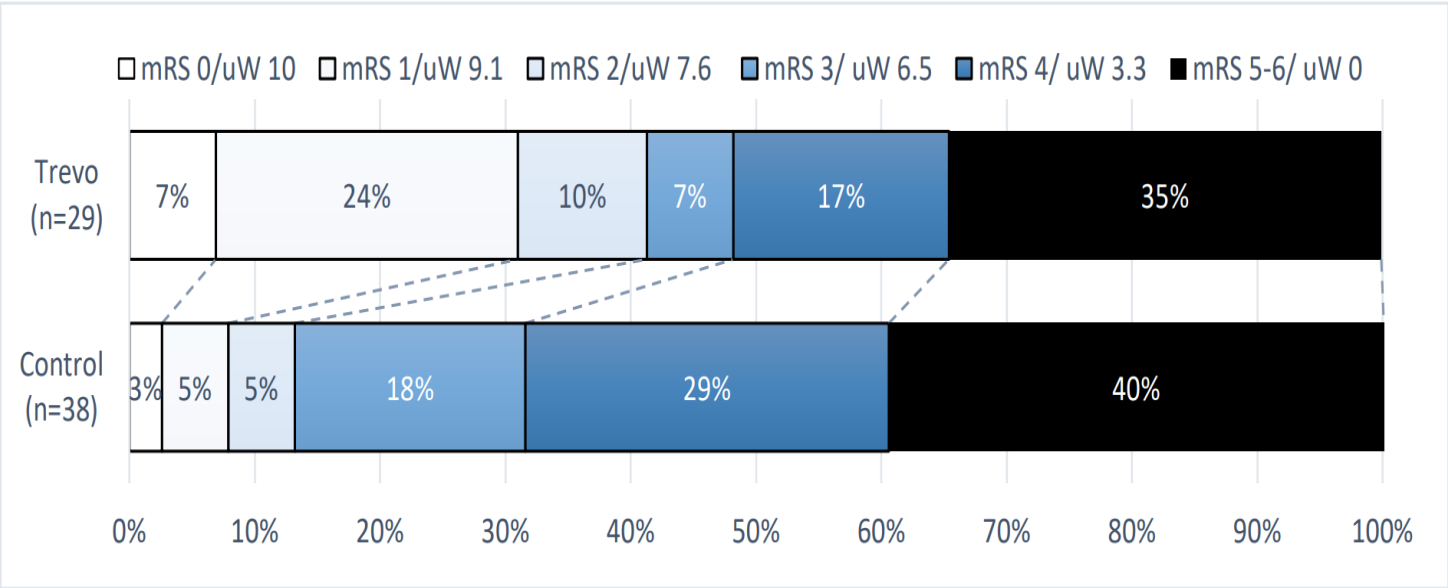
*Protocol advised to stop after oTICI 2b achieved

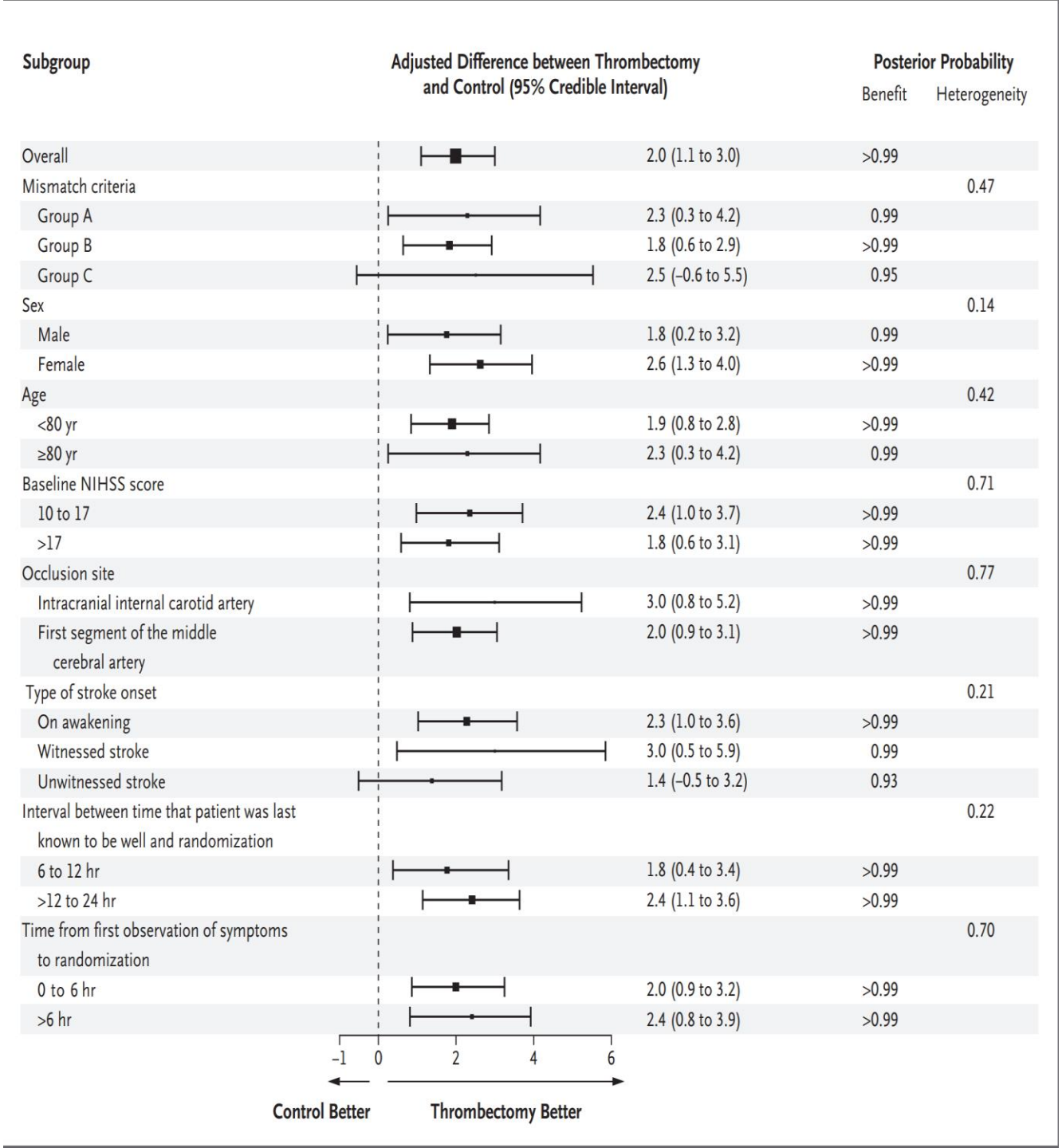

B Subgroups According to Time of Stroke Onset
Last Known to Be Well 6 to 12 Hr before Randomization
Thrombectomy (N=50)
14
22
18
10
6
30
Control (N=46)
7
7
6
11
37
33
0
10
20
30
40
50
60
70
80
90
100
Last Known to Be Well >12 to 24 Hr before Randomization
Thrombectomy (N=57)
5
23
16
16
19
21
Control (N=53)
4
21
32
40
2
2
0
10
20
30
40
50
60
70
80
90
100
Percent of Patients

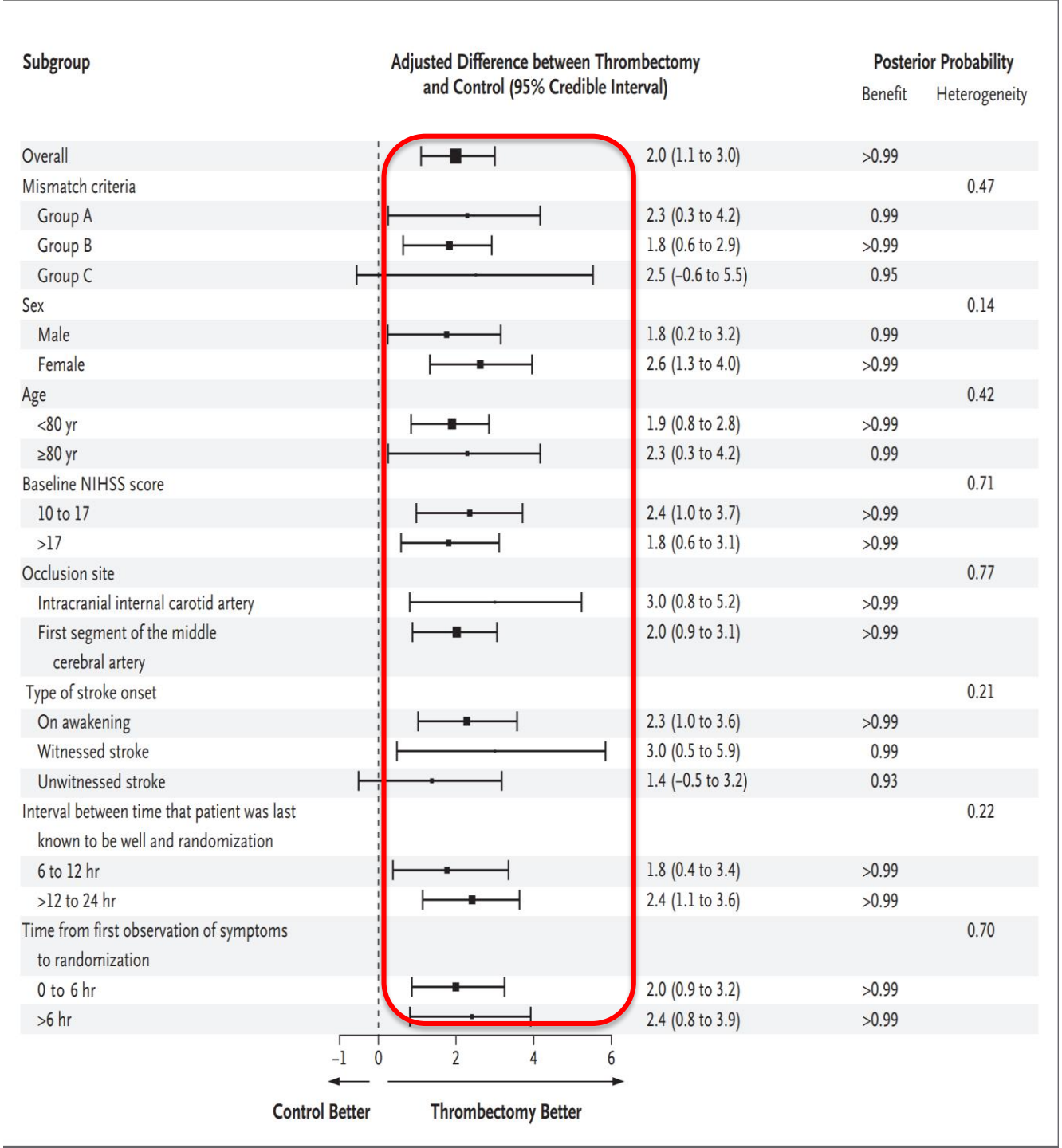
Wake up



Unwitnessed




Subgroup
Adjusted Difference between Thrombectomy and Control (95% Credible Interval)
Posterior Probability
Benefit
Heterogeneity
Overall
2.0 (1.1 to 3.0)
>0.99
Mismatch criteria
0.47
Group A
2.3 (0.3 to 4.2)
0.99
Group B
1.8 (0.6 to 2.9)
>0.99
Group C
2.5 (−0.6 to 5.5)
0.95
Sex
0.14
Male
1.8 (0.2 to 3.2)
0.99
Female
2.6 (1.3 to 4.0)
>0.99
Age
0.42
<80 yr
1.9 (0.8 to 2.8)
>0.99
≥80 yr
2.3 (0.3 to 4.2)
0.99
Baseline NIHSS score
0.71
10 to 17
2.4 (1.0 to 3.7)
>0.99
>17
1.8 (0.6 to 3.1)
>0.99
Occlusion site
0.77
Intracranial internal carotid artery
3.0 (0.8 to 5.2)
>0.99
First segment of the middle cerebral artery
2.0 (0.9 to 3.1)
>0.99
Type of stroke onset
0.21
On awakening
2.3 (1.0 to 3.6)
>0.99
Witnessed stroke
3.0 (0.5 to 5.9)
0.99
Unwitnessed stroke
1.4 (−0.5 to 3.2)
0.93
Interval between time that patient was last known to be well and randomization
0.22
6 to 12 hr
1.8 (0.4 to 3.4)
>0.99
>12 to 24 hr
2.4 (1.1 to 3.6)
>0.99
Time from first observation of symptoms to randomization
0.70
0 to 6 hr
2.0 (0.9 to 3.2)
>0.99
>6 hr
2.4 (0.8 to 3.9)
>0.99
−1
0
2
4
6
Control Better
Thrombectomy Better


Subgroup
Adjusted Difference between Thrombectomy and Control (95% Credible Interval)
Posterior Probability
Benefit
Heterogeneity
Overall
2.0 (1.1 to 3.0)
>0.99
Mismatch criteria
0.47
Group A
2.3 (0.3 to 4.2)
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>0.99
Group C
2.5 (−0.6 to 5.5)
0.95
Sex
0.14
Male
1.8 (0.2 to 3.2)
0.99
Female
2.6 (1.3 to 4.0)
>0.99
Age
0.42
<80 yr
1.9 (0.8 to 2.8)
>0.99
≥80 yr
2.3 (0.3 to 4.2)
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Baseline NIHSS score
0.71
10 to 17
2.4 (1.0 to 3.7)
>0.99
>17
1.8 (0.6 to 3.1)
>0.99
Occlusion site
0.77
Intracranial internal carotid artery
3.0 (0.8 to 5.2)
>0.99
First segment of the middle cerebral artery
2.0 (0.9 to 3.1)
>0.99
Type of stroke onset
0.21
On awakening
2.3 (1.0 to 3.6)
>0.99
Witnessed stroke
3.0 (0.5 to 5.9)
0.99
Unwitnessed stroke
1.4 (−0.5 to 3.2)
0.93
Interval between time that patient was last known to be well and randomization
0.22
6 to 12 hr
1.8 (0.4 to 3.4)
>0.99
>12 to 24 hr
2.4 (1.1 to 3.6)
>0.99
Time from first observation of symptoms to randomization
0.70
0 to 6 hr
2.0 (0.9 to 3.2)
>0.99
>6 hr
2.4 (0.8 to 3.9)
>0.99
−1
0
2
4
6
Control Better
Thrombectomy Better

The DAWN of a new era

FRAME OF REFERENCE

Dawn of a New Era for Stroke Treatment

Implications of the DAWN Study for Acute Stroke Care and Stroke Systems of Care

Mark J. Alberts, Martin D. Ollenschleger, Amre Nouh

Defuse 3 Trial

defuse·3

Hypothesis and Design

- Hypothesis: Stroke patients with MCA and/or ICA occlusion and salvageable tissue identified by CT/MR perfusion benefit from endovascular thrombectomy between 6-16 h.
- Design: Eligible patients randomized to thrombectomy (FDA cleared device) vs. medical management alone
- Endpoint: Modified Rankin Scale, blinded assessor, day 90
  Primary: ordinal shift analysis; Secondary: mRS 0-2

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Defuse 3 Trial

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Key Clinical Inclusion Criteria

Age	18 - 90 years
NIHSS	≥ 6
Pre-stroke mRS	0 - 2
Femoral puncture	6 - 16 hours

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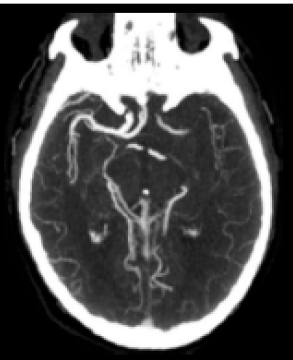
Key Neuroimaging Inclusion Criteria

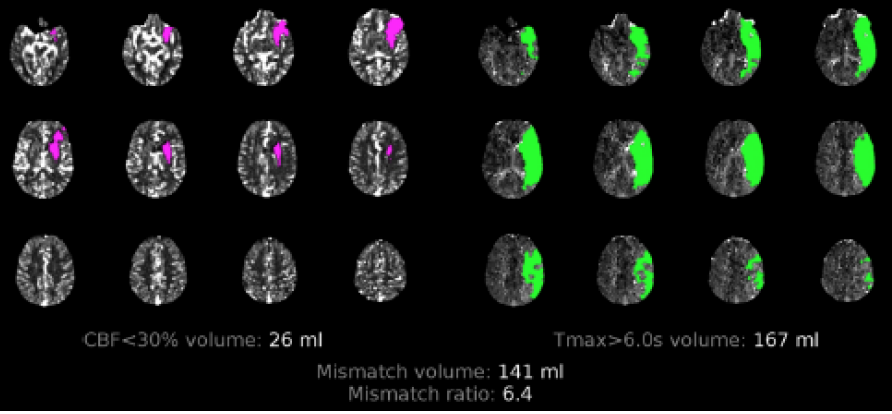
1) Occlusion of the ICA and/or MCA M1

AND

2) RAPID Target Mismatch Profile with core up to 70 ml

Substantially more patients eligible





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Defuse 3 Trial

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Early Termination

- A similar late-window study, DAWN, reported positive results in May 2017
- DEFUSE 3 was placed on hold for an early interim analysis
- Following this analysis, N = 182, the study was ended

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Patient Accrual

- 182 patients randomized in 1 yr
- Enrollment rate nearly double projected target
- Substantially faster than prior trials

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Defuse 3 Trial

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Baseline Characteristics

	Endovascular (N = 92)	Medical (N = 90)
Age, yr - median (IQR)	70 (59 - 78.5)	71 (59 - 80)
NIHSS score - median (IQR)	16 (10 -20)	16 (12 - 21)
Stroke onset to randomization - median (IQR)	10:53 (8:46-12:21)	10:44 (8:42-13:04)
Stroke onset wake-up (%)	53%	47%
Treatment with intravenous tPA (%)	11%	9%
Qualifying imaging: CT Perfusion	75%	71%
Ischemic core volume, ml - median (IQR)	9 (2 - 26)	10 (2 - 24)
Perfusion lesion (Tmax>6s) volume, ml - median (IQR)	115 (79-146)	116 (73 - 158)
Middle cerebral artery occlusion on baseline CTA / MRA	65%	60%

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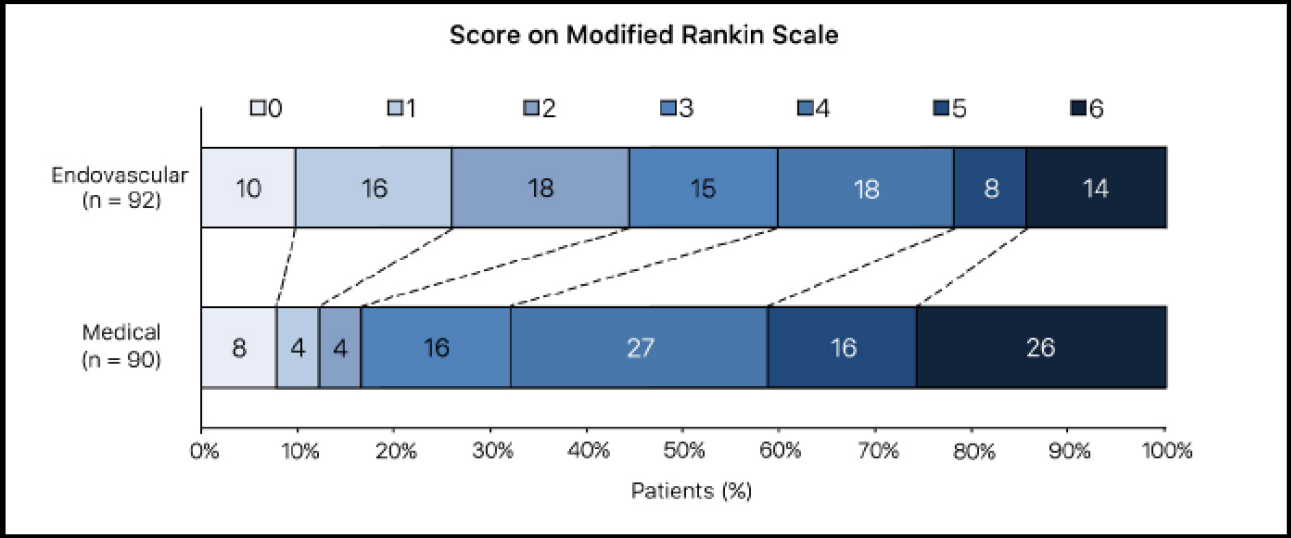
Results: Primary Outcome



Odds ratio:	2.8 (1.6 - 4.7)	P<0.0001
Adjusted odds ratio:	3.4 (2.0 - 5.8)	P=0.0004
Number needed to treat:	2	

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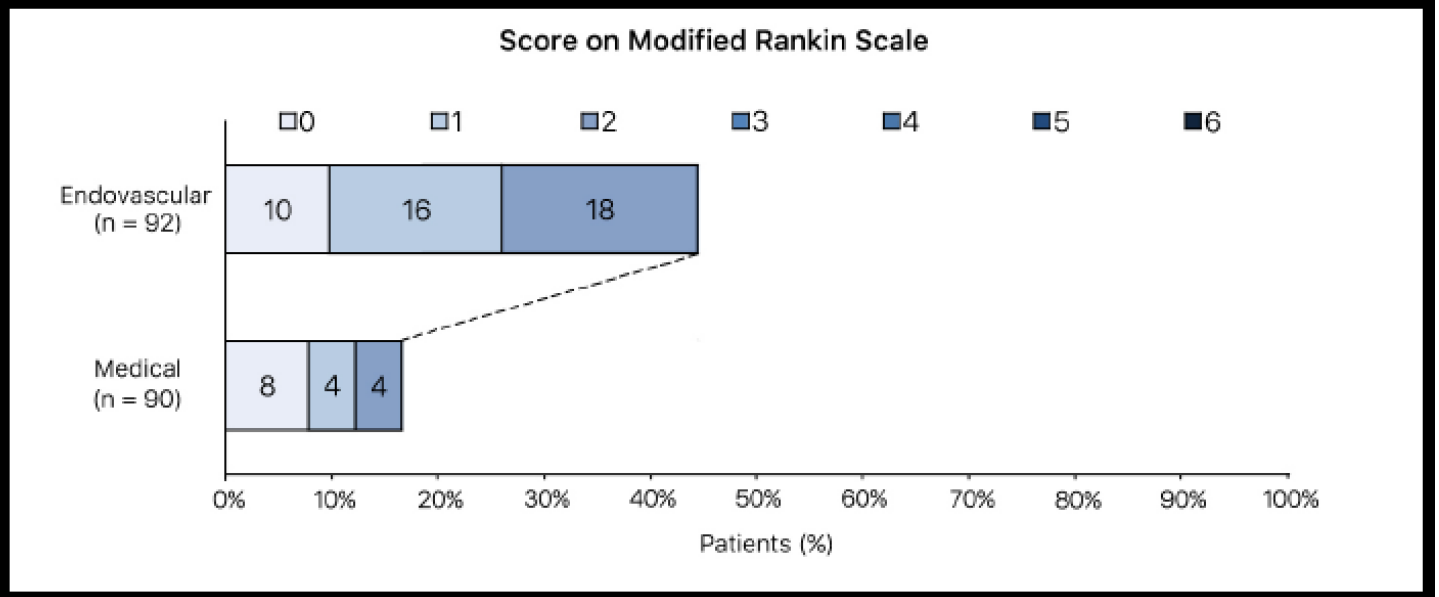
Secondary Outcome (mRS 0-2)



mRS 0-2 45% vs. 17% P<0.0001

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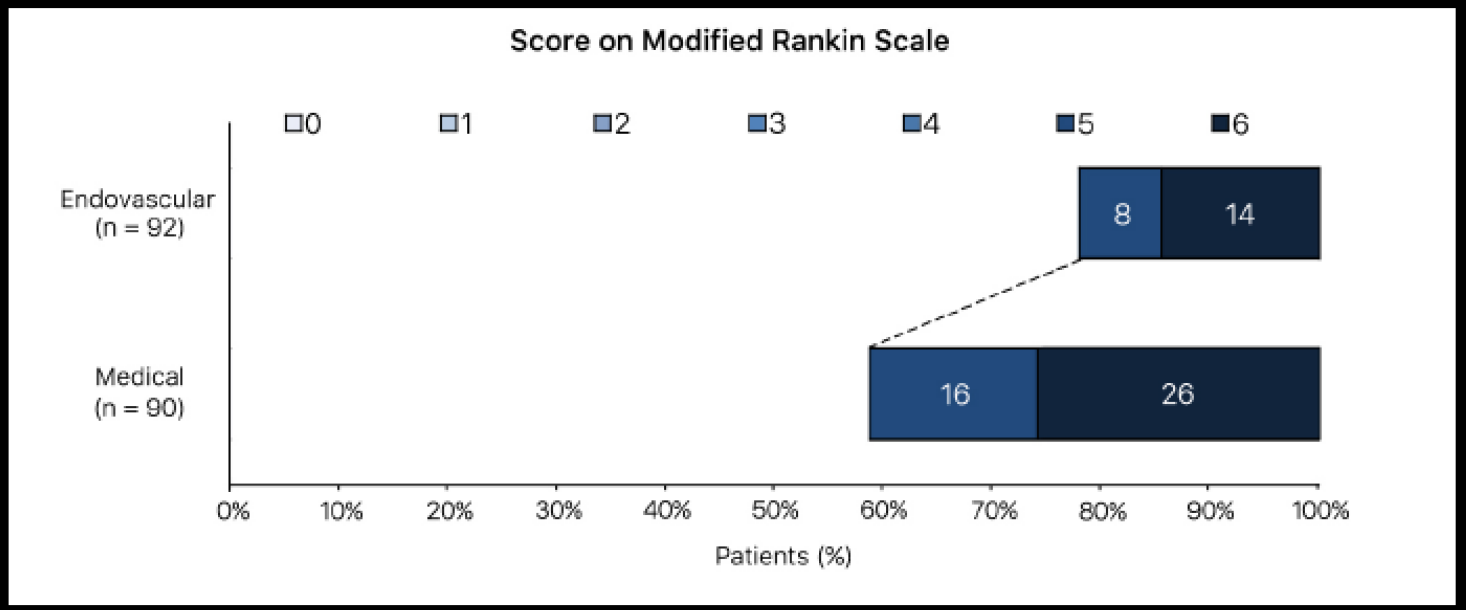
Severe disability/death (mRS 5-6)



mRS 5-6 22% vs. 42% P=0.0048

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Primary Safety Outcomes

	Endovascular	Medical	P-value
Symptomatic ICH*	6.5%	4.4%	0.75

* 5/6 patients with SICH died in endovascular vs. 2/4 in medical

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Primary Safety Outcomes

	Endovascular	Medical	P-value
Symptomatic ICH*	6.5%	4.4%	0.75
Death	14%	26%	0.05

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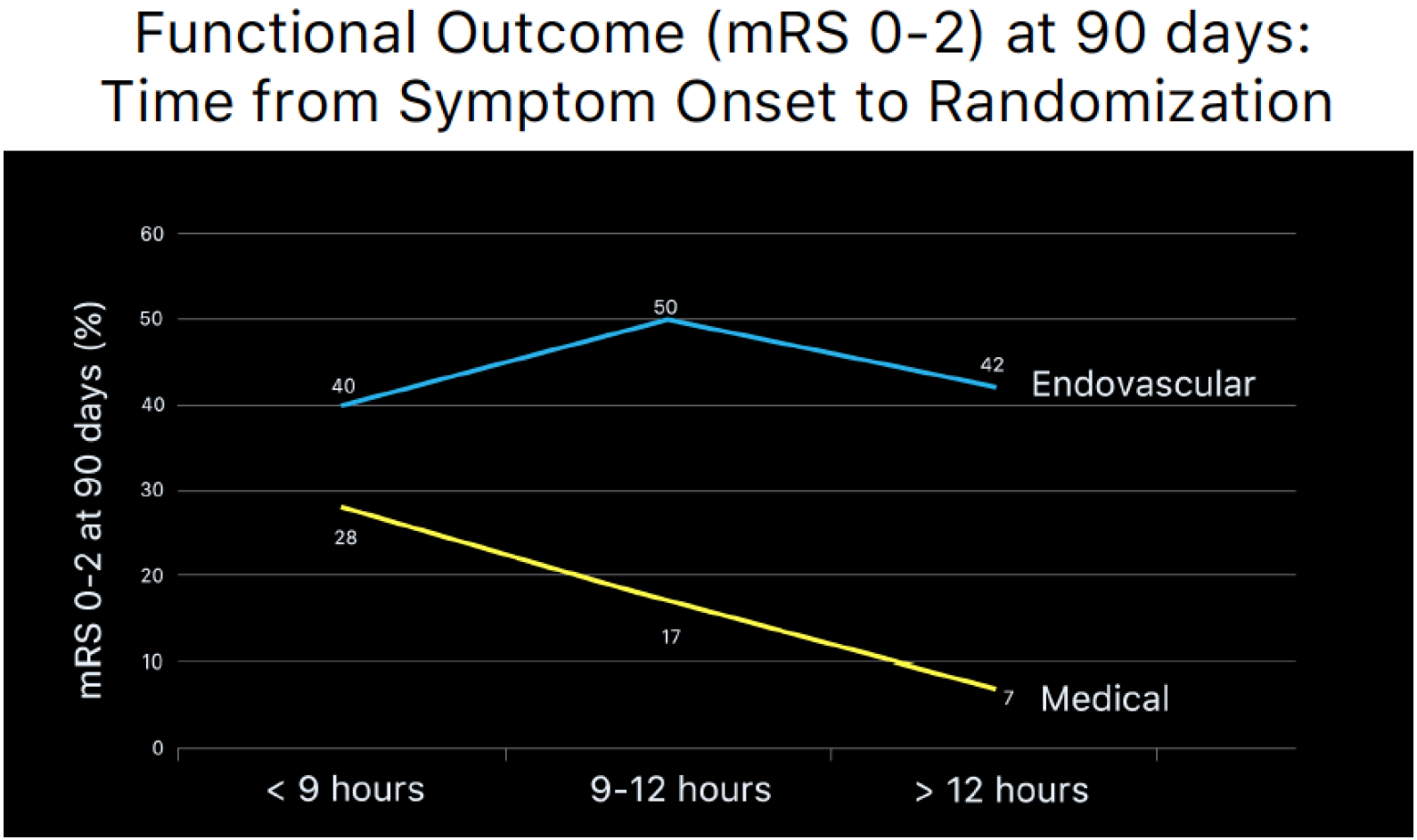
Wake-up vs. Witnessed onset

	Treatment effect mRS shift, OR (95% CI)
Wake-up	3.4 (1.6 - 7.4)
Witnessed onset*	3.4 (1.4 - 8.3)

*Median time to randomization 9.5 hours

Defuse 3 Trial



DAWN and DEFUSE 3 in practice

AHA/ASA Guideline

2015 AHA/ASA Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment

Endovascular Protocol and Patient Selection

"Patients eligible for intravenous rtPA should receive intravenous rtPA even if intra-arterial treatments are being considered."

Class I | Level of Evidence A | Unchanged Guideline

Patients should receive endovascular therapy with a stent retriever if they meet all the following criteria

a) prestroke mRS score 0 to 1,
b) acute ischemic stroke receiving intravenous r-tPA within 4.5 hours of onset according to guidelines from professional medical societies,
c) causative occlusion of the internal carotid artery or proximal MCA (M1),
d) age ≥18 years,
e) NIHSS score of ≥ 6,
f) ASPECTS of ≥ 6, and
g) treatment can be initiated (groin puncture) within 6 hours of symptom onset

Class I | Level of Evidence A | New Recommendation

Ovbiagele, and Dileep R. Yavagal. "2015 AHA/ASA Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association." American Heart Association Stroke Council. Stroke Published online June 29th 2015.

DAWN and DEFUSE 3 in practice

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

Time window

- 0 - 6h. Level 1A
- 6 – 16H. Level 1A. DAWN and DEFUSE 3
- 16 – 24h. Only DAWN Patients. Level 2A B-R.

DAWN and DEFUSE 3 in practice

Total AIS= 2667		DAWN Trial		DEFUSE-3 Trial

UPMC – 2667 AIS patients

Jadhav and Jovin, Stroke 2018

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LSW to Arrival Time (% of total=2667)	6-24 hours	792 (30%)	6-16 hours	451 (17%)
NIHSS Score (% of total=2667)	≥ 10	890 (33%)	≥ 6	1242 (47%)

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Patients meeting LSW to Arrival time and NIHSS Criteria (% of total=2667)		298 (11.2%)		285 (10.7%)
Presence of proximal anterior large vessel occlusion MCA-M1/ ICAT/ Intracranial IC occlusion with or without extracranial IC occlusion		155		133

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		45			47-58
Percentage of patients eligible for Trial enrollment (% of total=2667)		**1.7%**			**1.8-2.2%**
Patients meeting DAWN and DEFUSE-3 Criteria (% of total=2667)		**30 (1.1%)**			
Patients meeting DAWN and/or DEFUSE-3 criteria (% of total=2667)		**73 (2.7%)**			

Jadhav and Jovin, Stroke 2018

DAWN and DEFUSE 3 in practice

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Jadhav and Jovin, Stroke 2018

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Jadhav and Jovin, Stroke 2018

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Jadhav and Jovin, Stroke 2018

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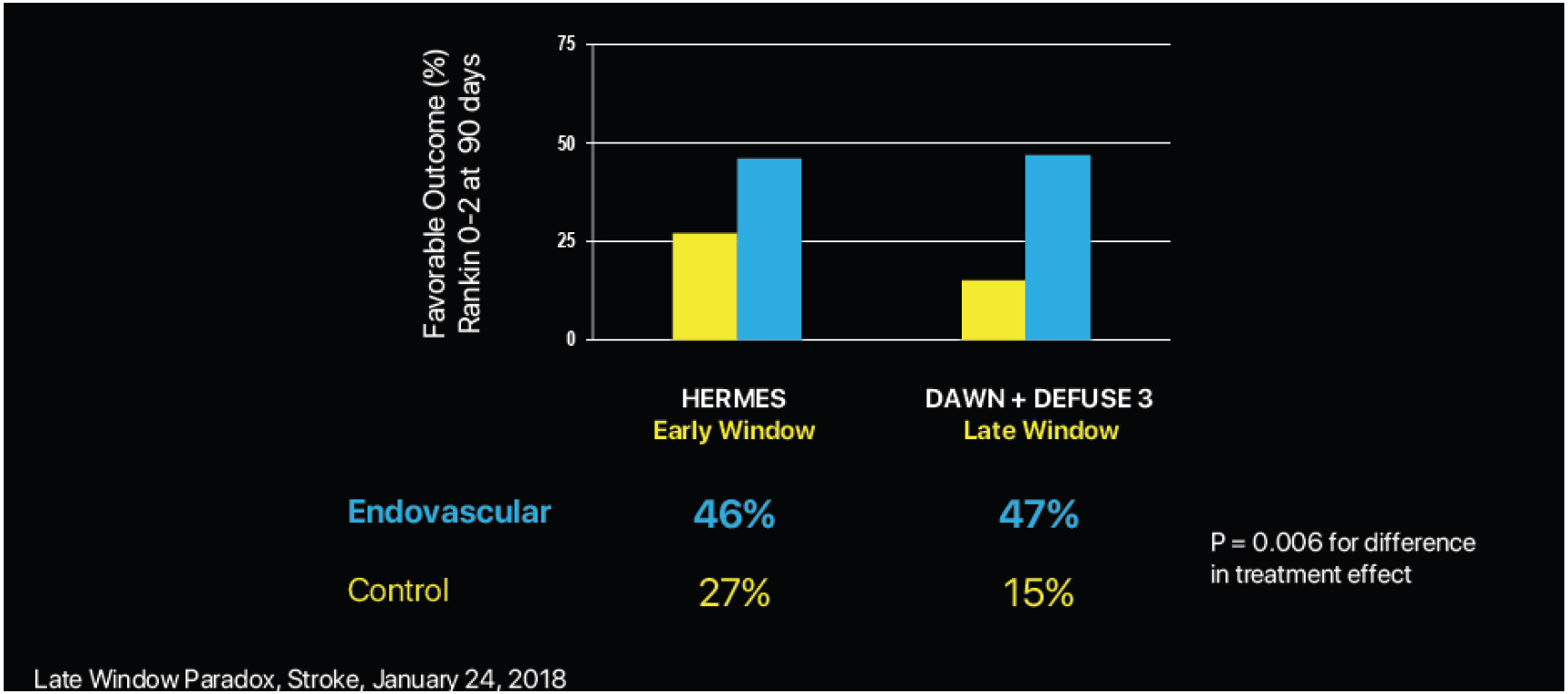
- Expanding treatment based on both DAWN and/ or DEFUSE-3 criteria would further broaden treatment eligibility to 9.2% of all patients presenting in the 6-24-hour time window.
- A third of eligible patients are elderly (>80 years) and nearly half present as wake-up strokes.

Jadhav and Jovin, Stroke 2018

Late presenter paradox



Acute Stroke Treatment 2018

- Extended time window is there!

Acute Stroke Treatment 2018

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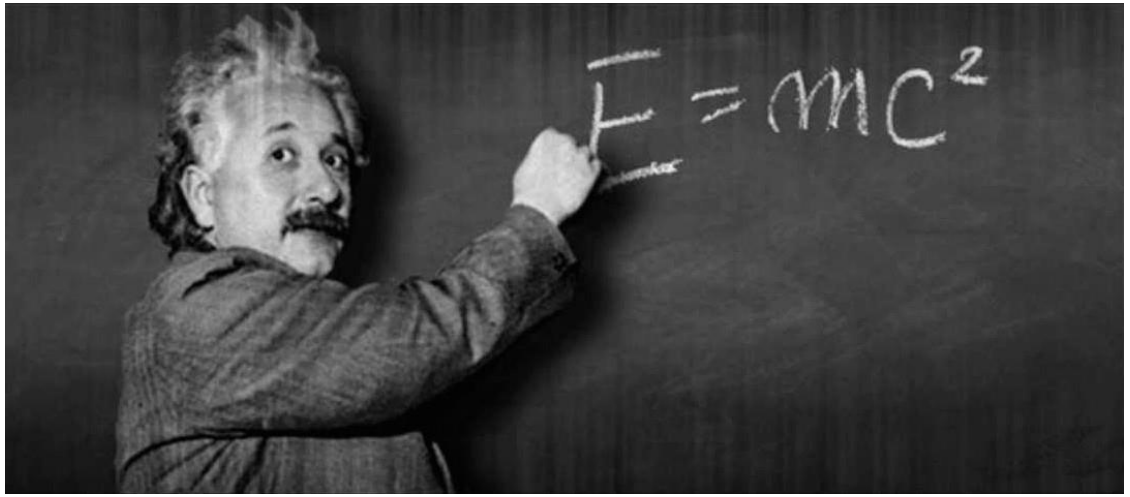
- Time in Stroke is very important but Onset time is relative!



AIS 2018

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  - Relative to:
    - Collaterals
    - Brain tissue/BBB
    - Age, vascular risk factors

AIS 2018

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  - Relative to:
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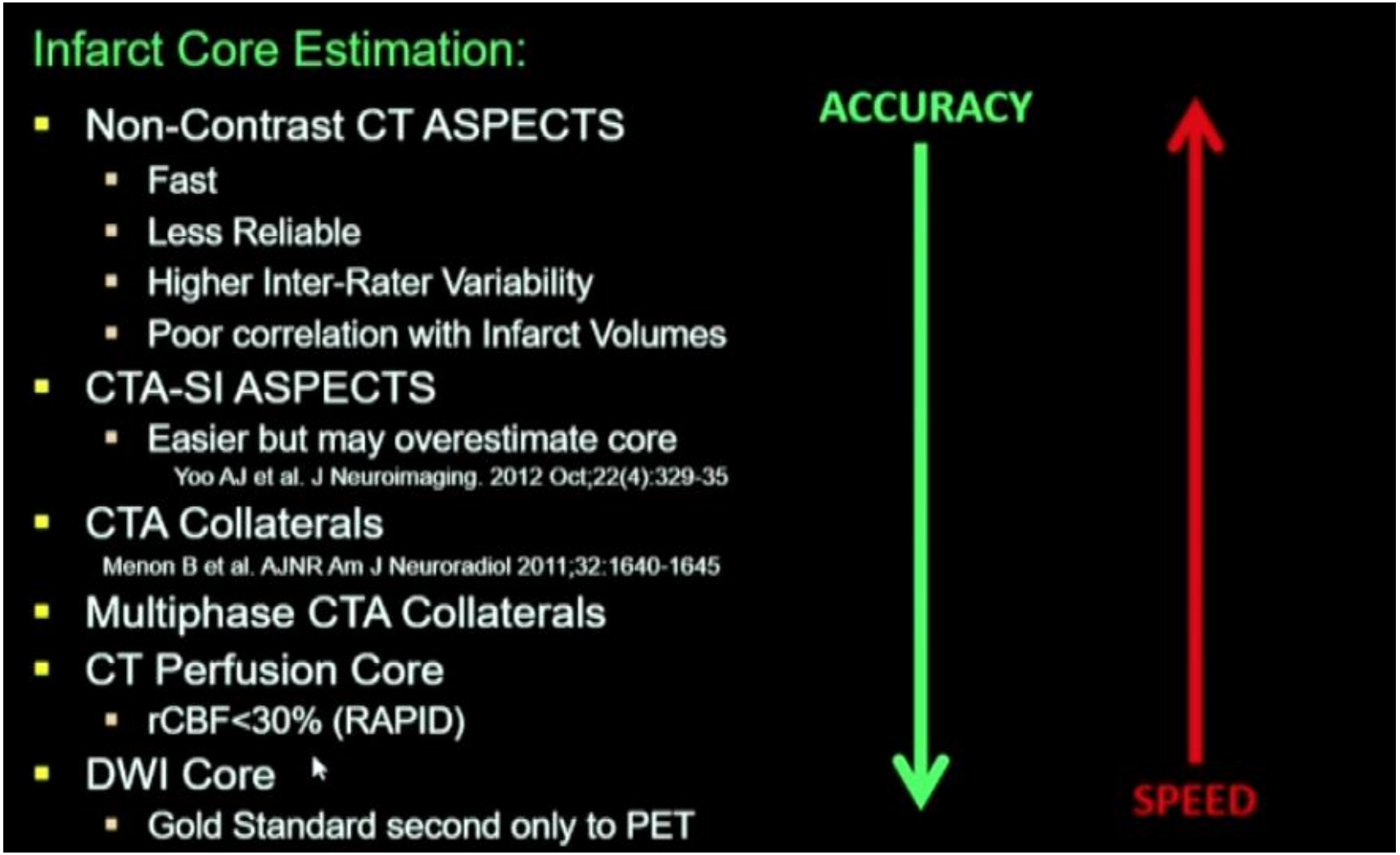
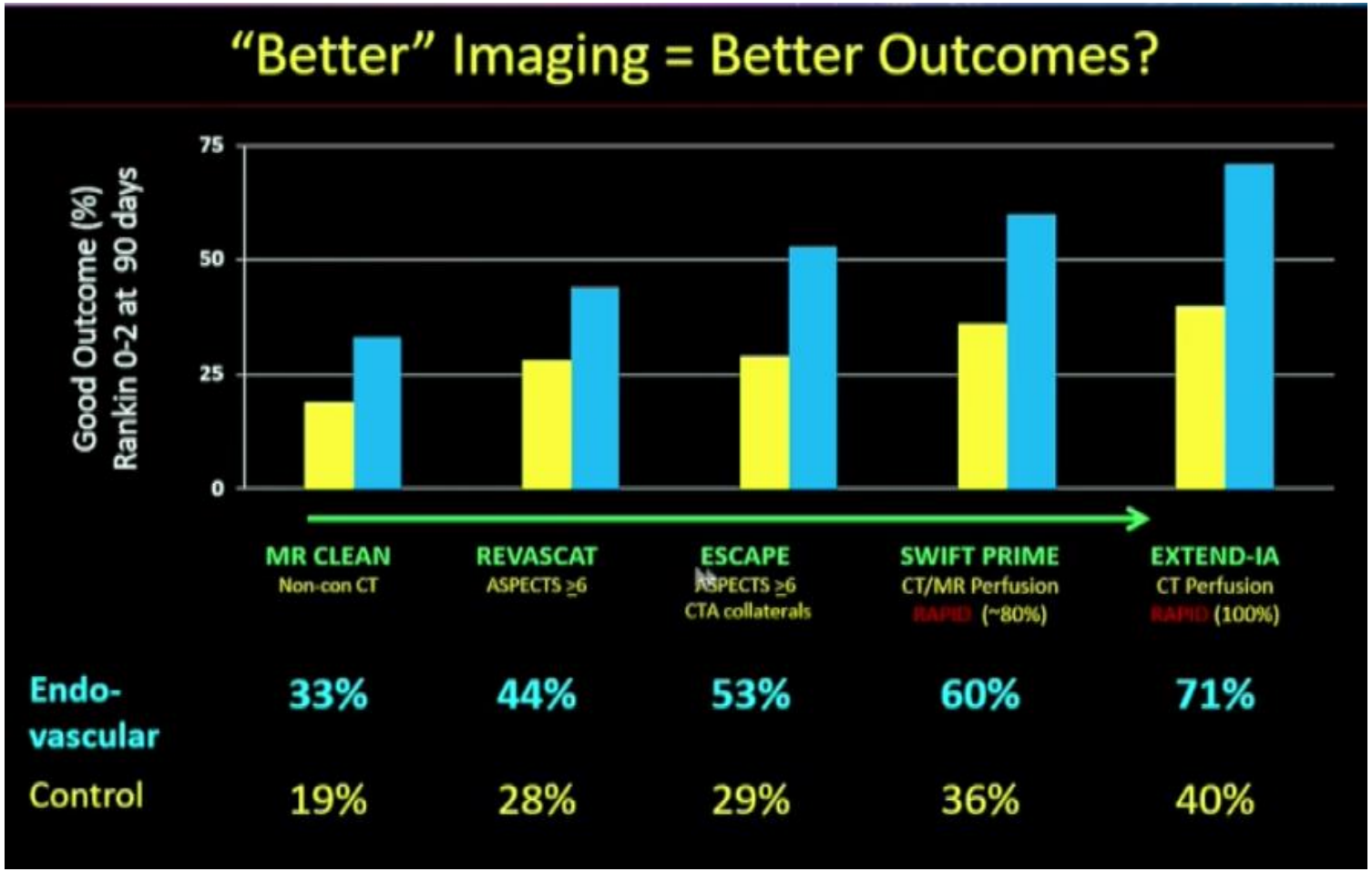
    - Age, vascular risk factors
- Imaging selection with …?
  - DAWN and DEFUSE 3 … Perfusion or MRI DWI to identify the core
  - AHA guidelines: Follow DAWN and DEFUSE 3 inclusion criteria
  - Daily practice: ??

Imaging selection



Nogueira

Imaging selection



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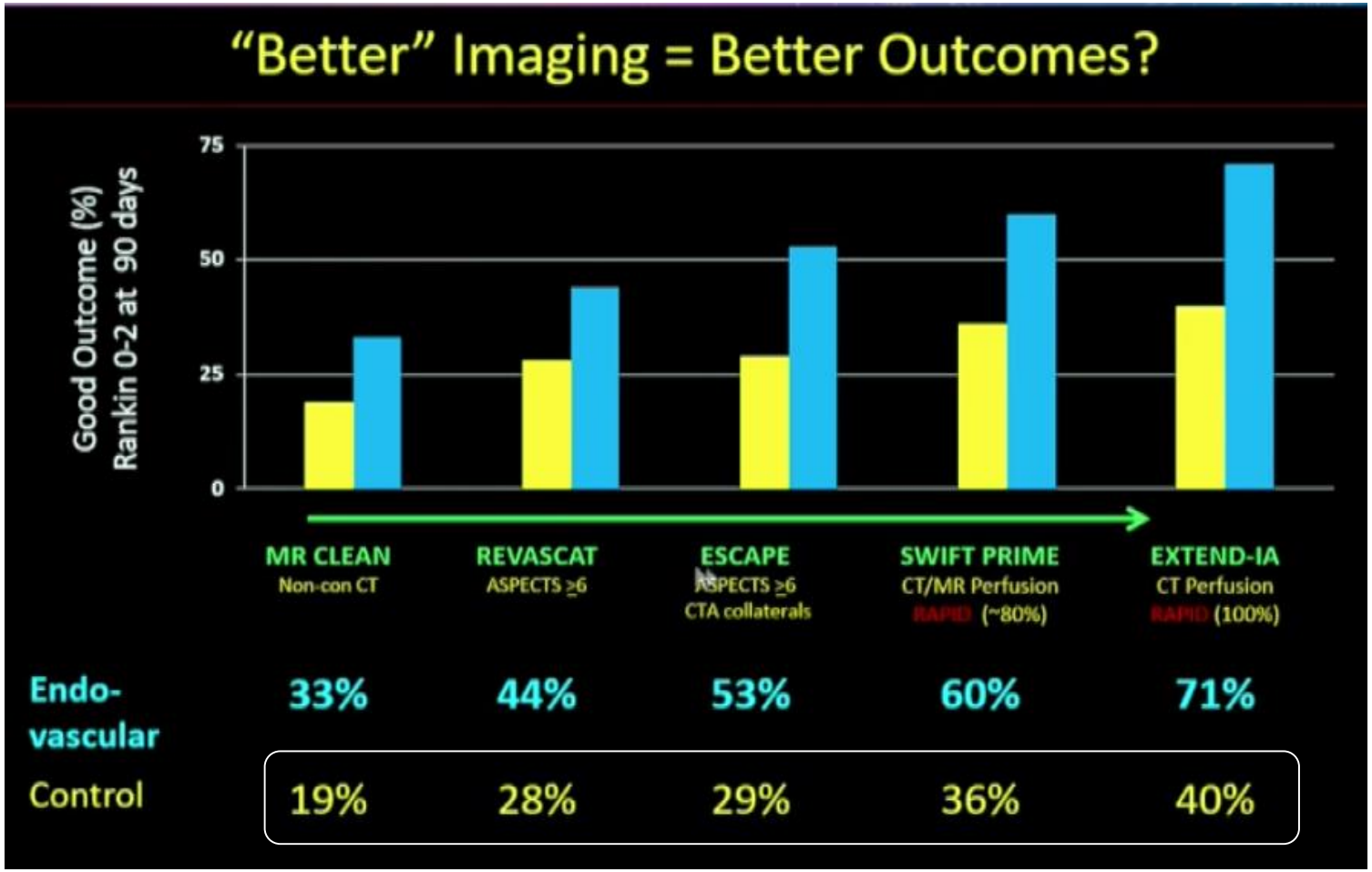

Nogueira

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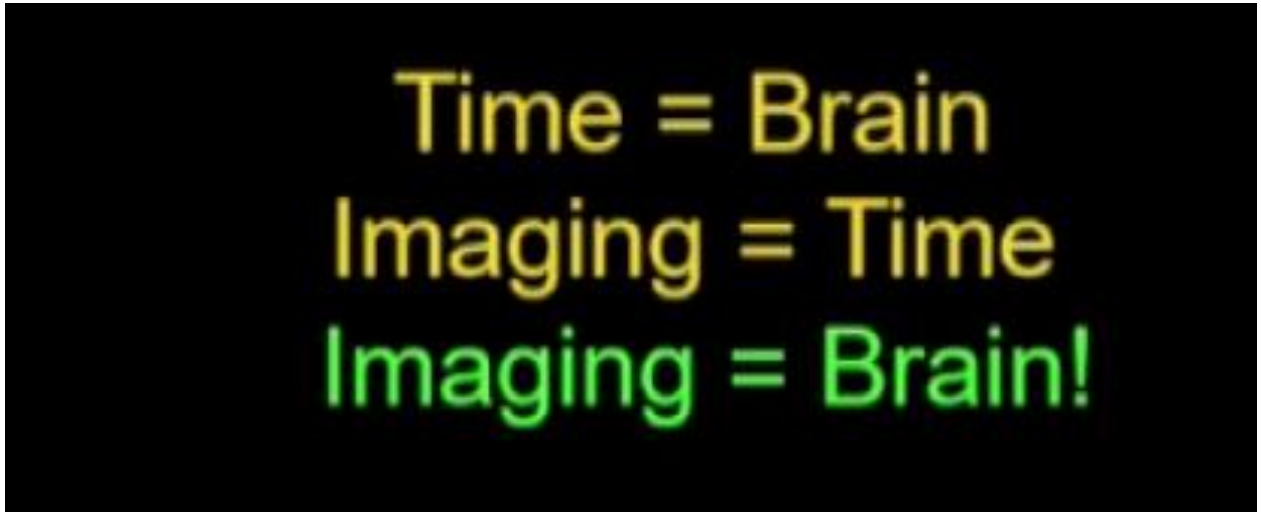

Jovin

Stroke treatment: Exciting times!!

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- Move fast if patient qualify for EVT.
- Stroke networks and systems organization have to be consistent with new trials and guidelines.

STROKE TEAM

- Interventional Neuroradiology
  - Ronit Agid
  - Richard Farb
  - Timo Krings
  - Vitor Mendes Pereira
  - Endovascular fellows (3)
- Neurosurgery
  - Michael Tymianski
  - Ivan Radovanovic
  - Vascular neurosurgical fellows
- Vascular Neurology
  - Frank Silver
  - Lee-anne Casabon
  - Cheryl Jagobin
  - Martin del Campo
  - Alexandra Pikula
  - Joanna Schaafsma
  - Vascular fellows (2)
  - Neurology resident in rotation
  - Stroke nurses (5)

Thanks for your attention!!

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