Recent advances in Hyperacute and Acute Stroke Care

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Disclosures

- I have no commercial disclosures or conflicts of interest

Stroke Care Continues to Evolve

- Tenecteplase
- Thrombolysis after 4.5 hours
- EVT for large core infarction

Tenecteplase vs Tissue plasminogen activator

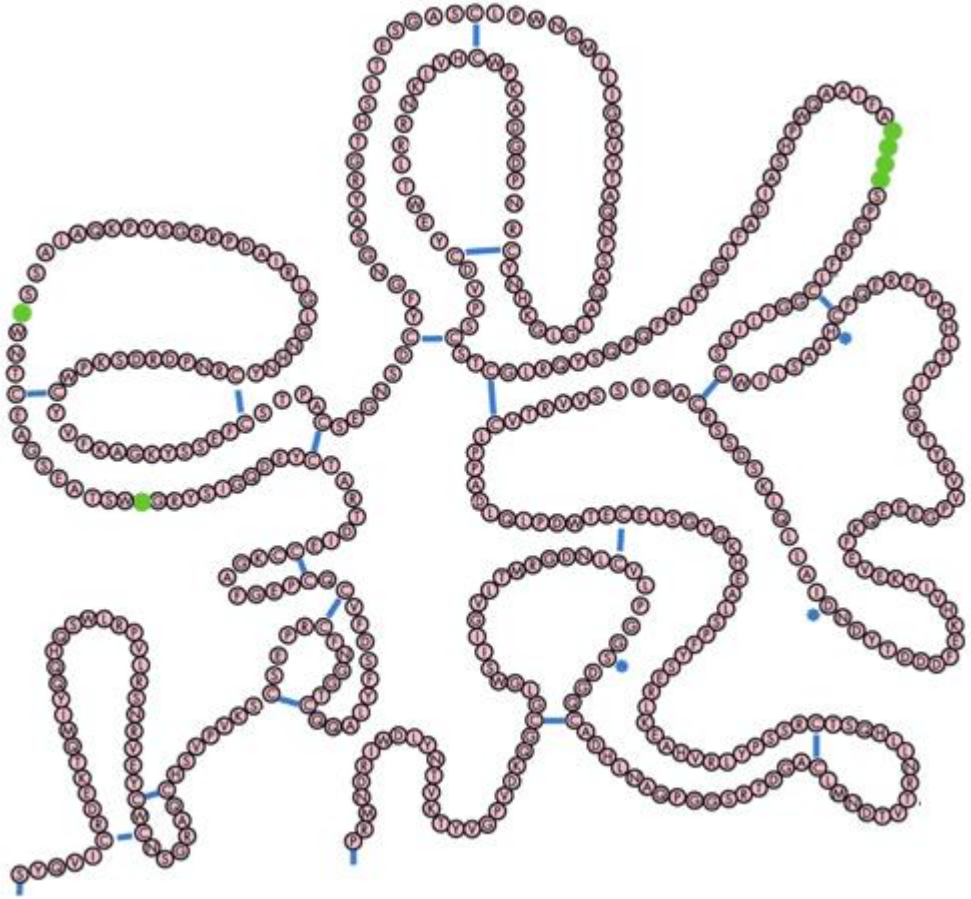
- IV tPA has been the standard of care for acute ischemic stroke within 4.5 hours for many years

- But IV tPA administration can be labor intensive and complex, one of the factors that leads to under-utilization

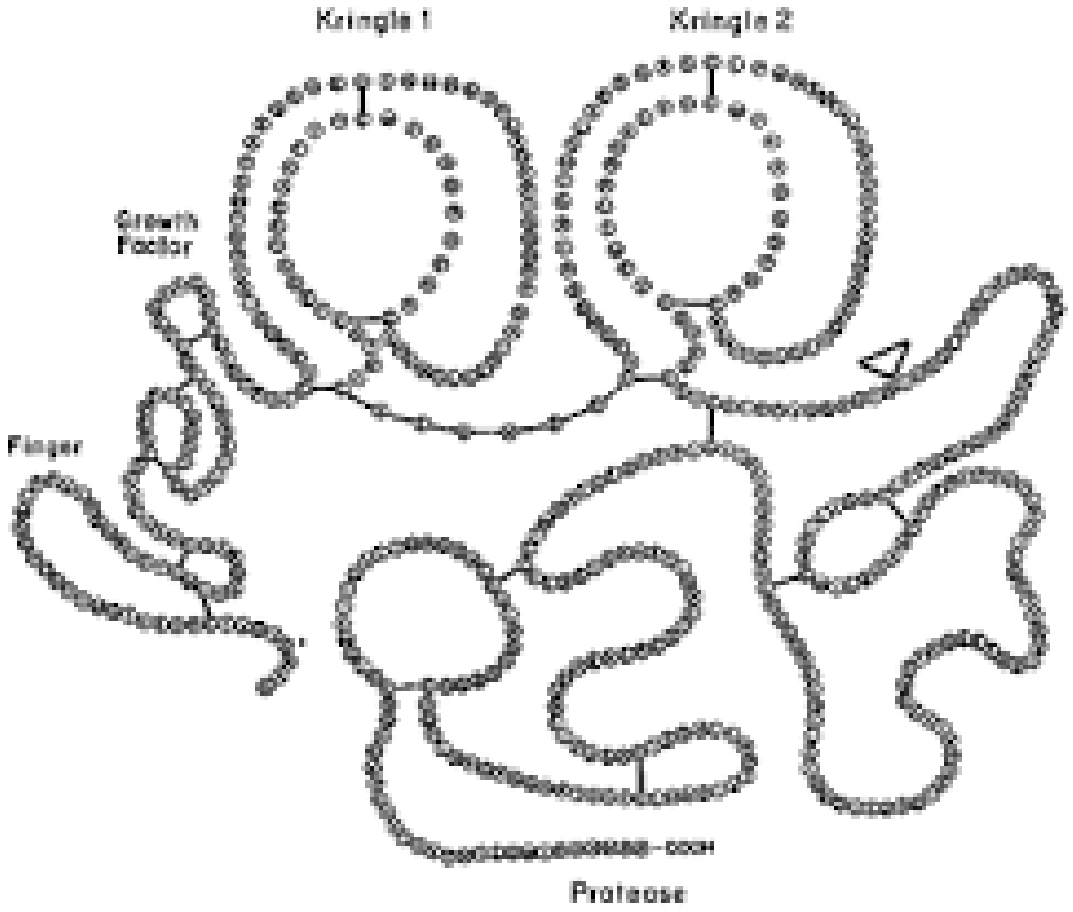
- Tenecteplase, also known as TNK, is similar to tPA but has the advantage that it can be delivered in a 5 second IV bolus without the need to program an infusion pump

TNK vs tPA

Structure of TNK



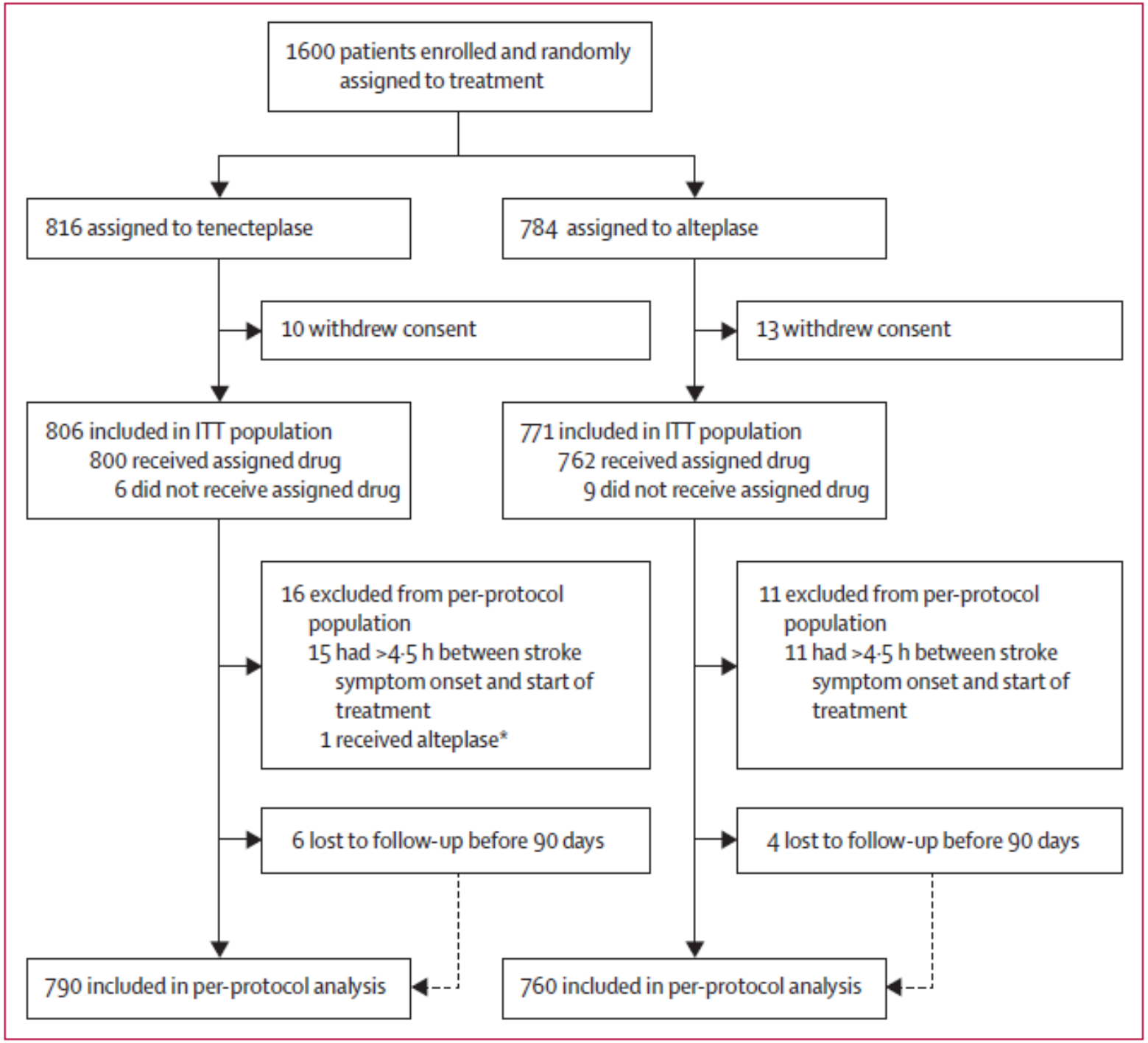
Structure of tPA



Intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial

Bijoy K Menon, Brian H Buck, Nishita Singh, Yan Deschaintre, Mohammed A Almekhlafi, Shelagh B Coutts, Sibi Thirunavukkarasu, Houman Khosravani, Ramana Appireddy, Francois Moreau, Gord Gubitz, Aleksander Tkach, Luciana Catanese, Dar Dowlatshahi, George Medvedev, Jennifer Mandzia, Aleksandra Pikula, Jai Shankar, Heather Williams, Thalia S Field, Alejandro Manosalva, Muzaffar Siddiqui, Atif Zafar, Oje Imoukhuede, Gary Hunter, Andrew M Demchuk, Sachin Mishra, Laura C Gioia, Shirin Jalini, Caroline Cayer, Stephen Phillips, Elsadig Elamin, Ashkan Shoamanesh, Suresh Subramaniam, Mahesh Kate, Gregory Jacquin, Marie-Christine Camden, Faysal Benali, Ibrahim Alhabli, Fouzi Bala, MacKenzie Horn, Grant Stotts, Michael D Hill, David J Gladstone, Alexandre Poppe, Arshia Sehgal, Qiao Zhang, Brendan Cord Lethebe, Craig Doram, Ayoola Ademola, Michel Shamy, Carol Kenney, Tolulope T Sajobi, Richard H Swartz, for the AcT Trial Investigators

www.thelancet.com **Published online June 29, 2022** **https://doi.org/10.1016/S0140-6736(22)01054-6**



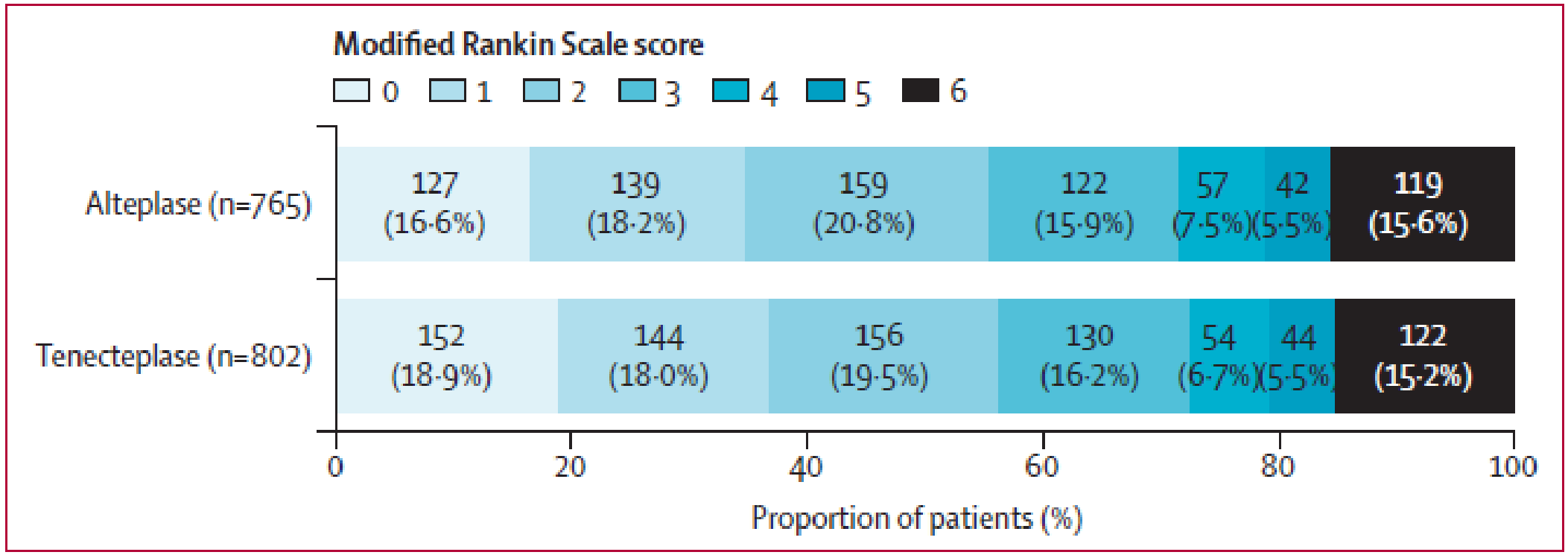
32% of TNK and 32.1% of tPA patients underwent EVT as well

	Tenecteplase group (n=806)	Alteplase group (n=771)
Age, years	74 (63–83)	73 (62–83)
Sex		
Female	382 (47·4%)	373 (48·4%)
Male	424 (52·6%)	398 (51·6%)
Baseline NIHSS score (n=1569)	9 (6–16)	10 (6–17)
Baseline NIHSS score categories		
<8	325/803 (40·5%)	294/766 (38·4%)
8–15	247/803 (30·8%)	256/766 (33·4%)
>15	231/803 (28·8%)	216/766 (28·2%)
Workflow times, min		
Stroke symptom onset to hospital arrival (n=1560)	82 (54–140)	83 (55–138)
Stroke symptom onset to randomisation (n=1570)	121 (85–179)	123 (88–179)
Door (hospital arrival) to baseline CT (n=1561)	15 (12–21)	16 (12–22)
Stroke symptom onset to needle (intravenous thrombolysis start; n=1562)	128 (93–186)	131 (95–188)
Door (hospital arrival) to needle (intravenous thrombolysis start; n=1556)	36 (27–49)	37 (29–52)
Baseline CT to arterial puncture (in patients undergoing EVT; n=505)	60 (43–88)	58 (41–85)
Arterial puncture to successful reperfusion (in patients undergoing EVT; n=445)	31 (19–47)	27 (17–45)

Door-needle time is fast with either TNK or tPA.

Patients were treated without major delay in both treatment arms.

Primary Outcome: mRS 0-1 at 90 days



AcT trial safety outcomes

	Tenecteplase (n=800)	Alteplase (n=763)
Death within 90 days	122/796 (15.3%)	117/758 (15.4%)
24h symptomatic ICH	27/800 (3.4%)	24/763 (3.2%)
Orolingual angio-edema	9/800 (1.1%)	9/763 (1.2%)
Extracranial bleeding requiring blood transfusions	6/800 (0.8%)	6/763 (0.8%)
Imaging-identified ICH	154/800 (19.3%)	157/763 (20.6%)

What does this mean for stroke care in our region?

- Kingston Health Sciences Centre was the first site in Ontario to start using TNK instead of tPA for acute ischemic stroke within 4.5 hours of onset
- Many sites across Ontario and Canada have also started using TNK instead of tPA
- In Ontario, this may have implications on ambulance transport from District Stroke Centres to Regional Stroke Centres for patients who require EVT in addition to TNK.

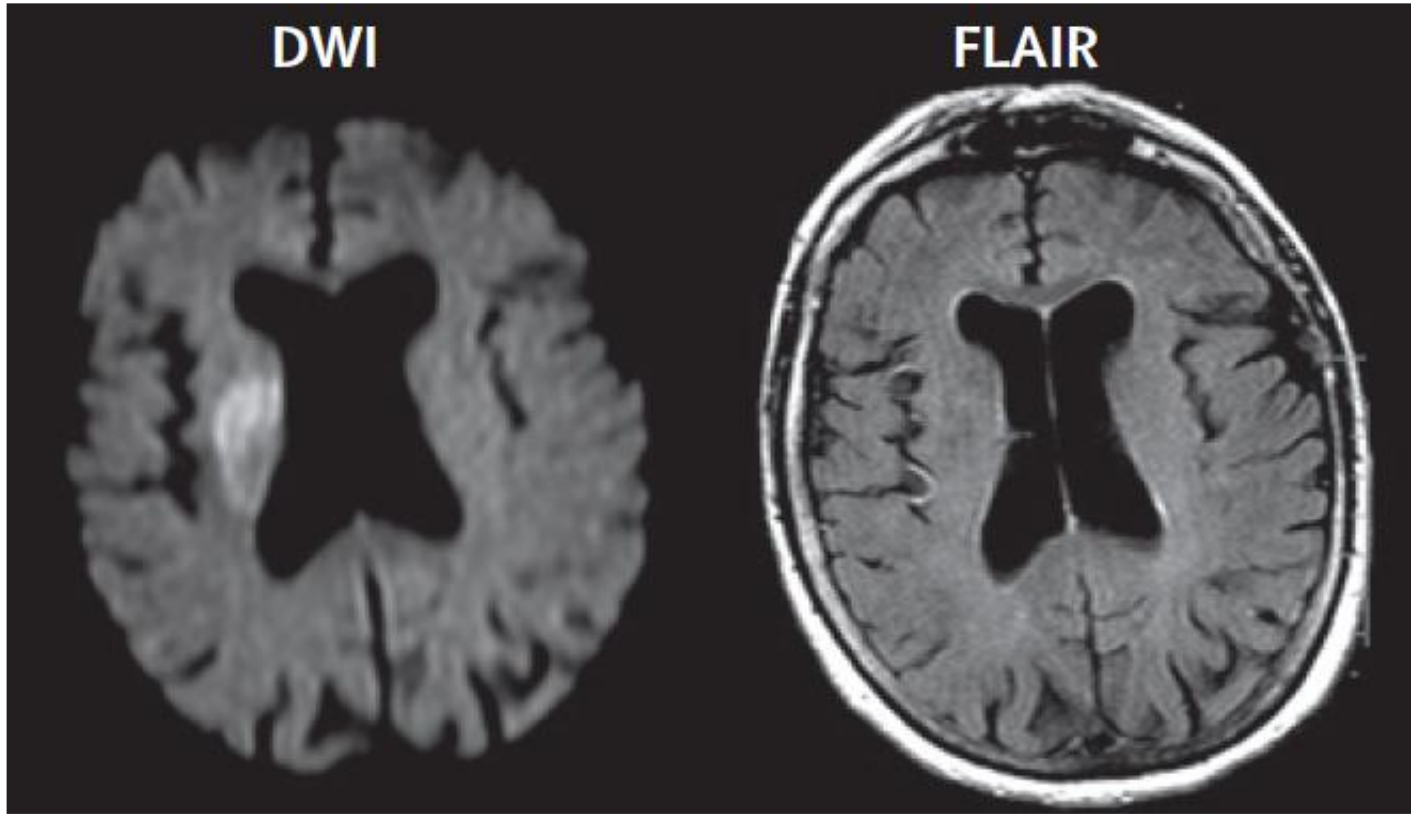
Thrombolysis for stroke presentation > 4.5 hours after onset

- IV thrombolysis (either tPA or TNK) for acute ischemic stroke is standard for patients within 4.5 hours of onset

- But many patients present to the ER just outside of this window, or they are “wake-up strokes” who may have had stroke just before waking

- With advanced imaging techniques such as MRI or CT perfusion, some of these patients may be appropriate for intravenous thrombolysis

The use of MRI to screen “wake-up stroke” patients



Lancet Neurol 2011; 10: 978–86

A positive DWI lesion and a negative FLAIR sequence has a 78% to 93% specificity and approximately 65% sensitivity to detect that stroke onset was within 4.5 hours (e.g., *Lancet Neurol* 2011; 10:978 and *Radiology* 2010; 257:782)

MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset

G. Thomalla, C.Z. Simonsen, F. Boutitie, G. Andersen, Y. Berthezene, B. Cheng, B. Cheripelli, T.-H. Cho, F. Fazekas, J. Fiehler, I. Ford, I. Galinovic, S. Gellissen, A. Golsari, J. Gregori, M. Günther, J. Guibernau, K.G. Häusler, M. Hennerici, A. Kemmling, J. Marstrand, B. Modrau, L. Neeb, N. Perez de la Ossa, J. Puig, P. Ringleb, P. Roy, E. Scheel, W. Schonewille, J. Serena, S. Sunaert, K. Villringer, A. Wouters, V. Thijs, M. Ebinger, M. Endres, J.B. Fiebach, R. Lemmens, K.W. Muir, N. Nighoghossian, S. Pedraza, and C. Gerloff, for the WAKE-UP Investigators*

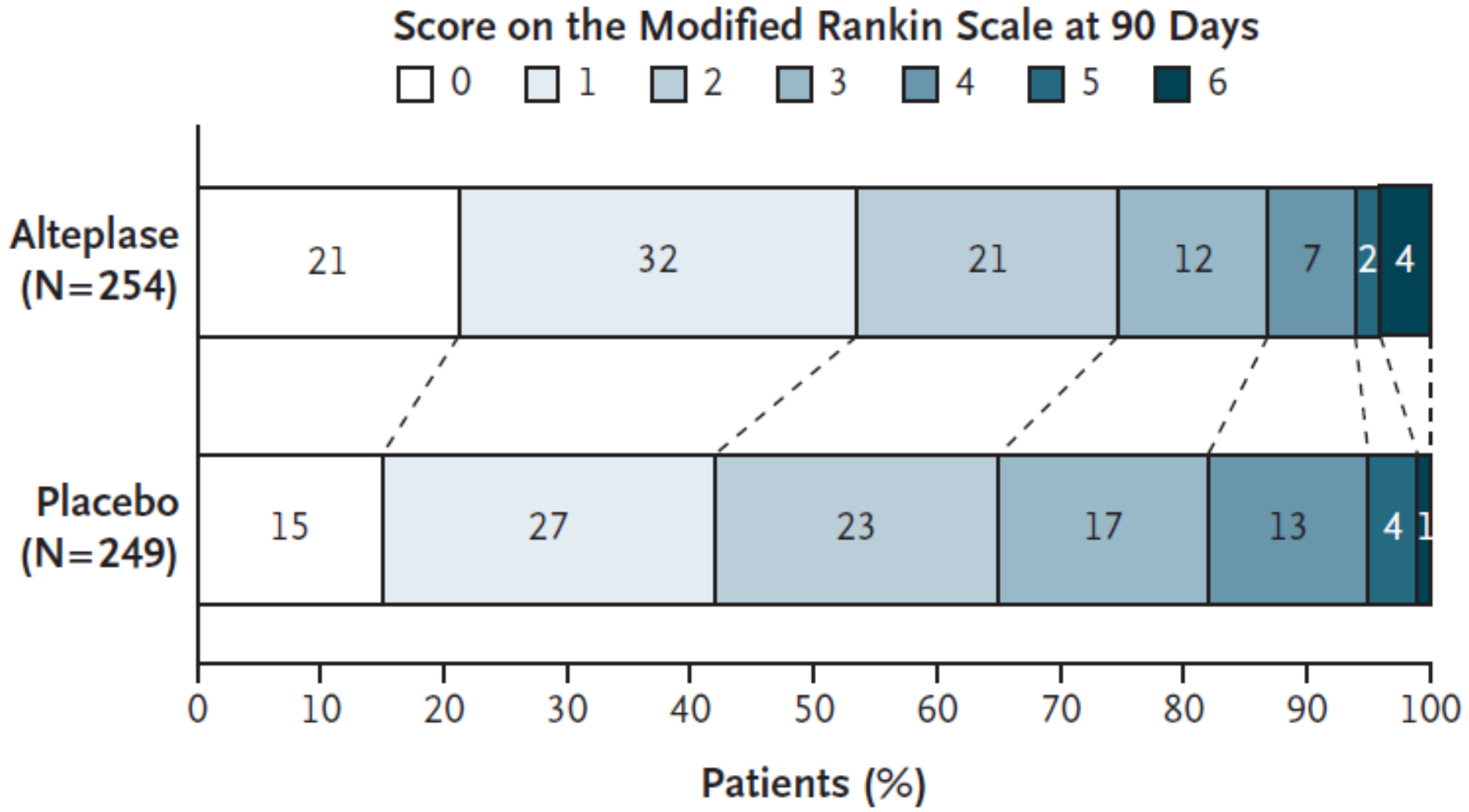
N ENGL J MED 379;7 NEJM.ORG AUGUST 16, 2018

The New England Journal of Medicine

Patients with DWI-FLAIR mismatch, n=503

Alteplase (n=254) vs placebo (n=249)

Favorable outcome defined as mRS 0-1 at 90 days



Modified Rankin Scale score of 0 or 1: independent with no or minimal deficit.

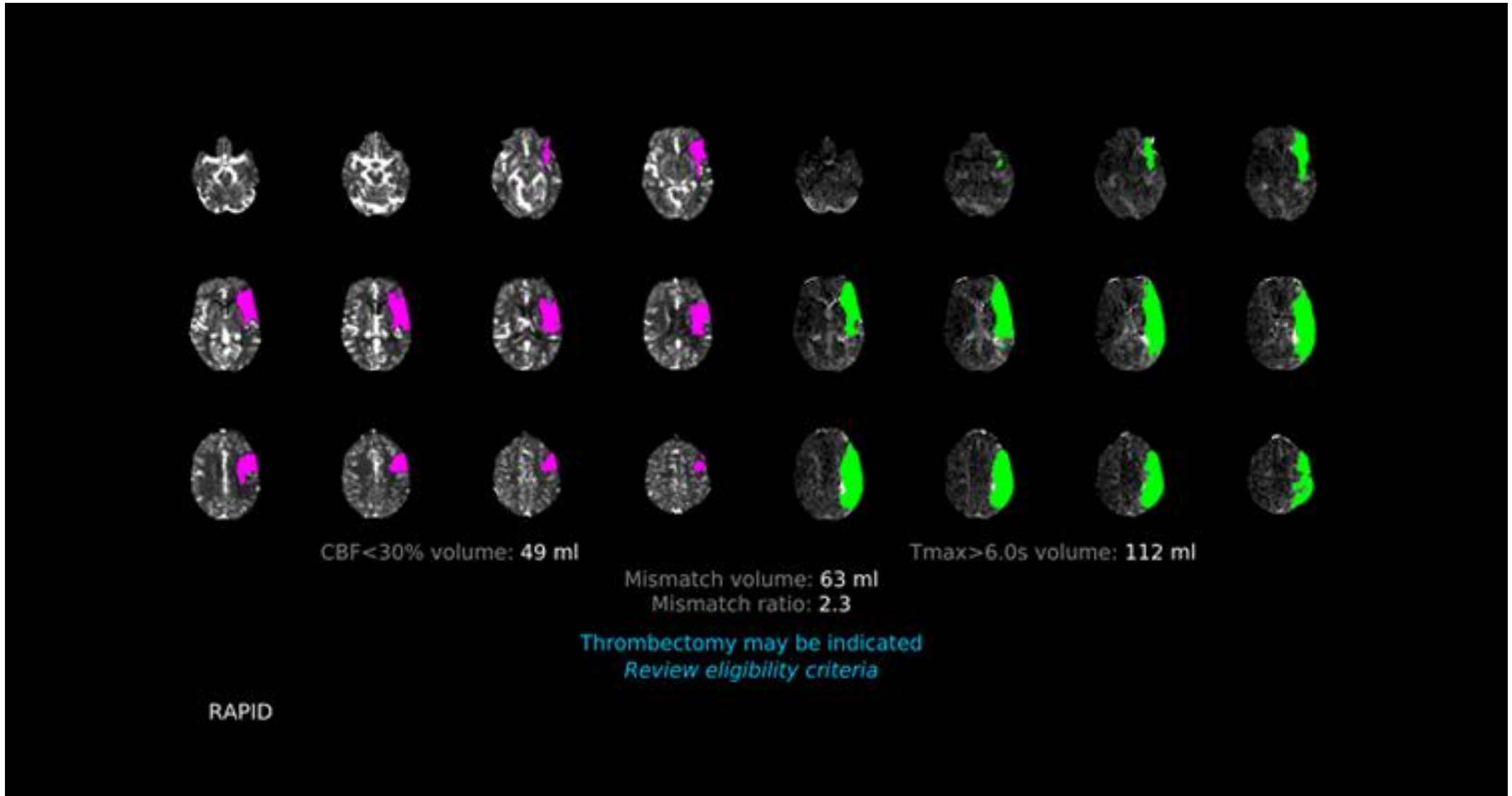
Favorable outcome in **53.3% of Alteplase group** vs 41.8% of Placebo group.

But what if you don’t have MRI?

- But most hospitals are unable to do MRI 24/7/365, so the WAKE-UP trial result can’t be widely applied

- CT perfusion is becoming more widely adopted and is available in many Ontario hospitals, including Kingston General Hospital and Belleville General Hospital

CT perfusion

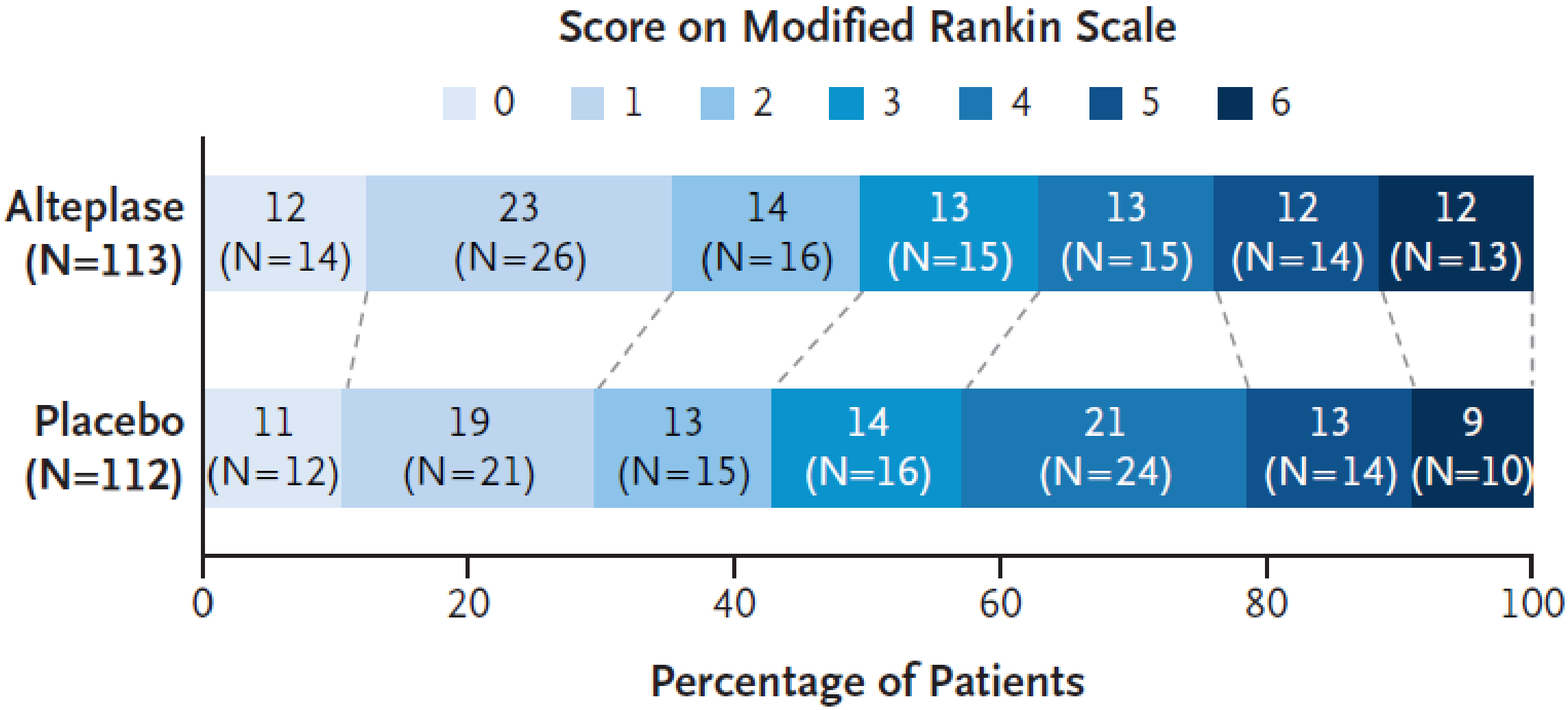


Thrombolysis Guided by Perfusion Imaging up to 9 Hours after Onset of Stroke

H. Ma, B.C.V. Campbell, M.W. Parsons, L. Churilov, C.R. Levi, C. Hsu, T.J. Kleinig, T. Wijeratne, S. Curtze, H.M. Dewey, F. Miteff, C.-H. Tsai, J.-T. Lee, T.G. Phan, N. Mahant, M.-C. Sun, M. Krause, J. Sturm, R. Grimley, C.-H. Chen, C.-J. Hu, A.A. Wong, D. Field, Y. Sun, P.A. Barber, A. Sabet, J. Jannes, J.-S. Jeng, B. Clissold, R. Markus, C.-H. Lin, L.-M. Lien, C.F. Bladin, S. Christensen, N. Yassi, G. Sharma, A. Bivard, P.M. Desmond, B. Yan, P.J. Mitchell, V. Thijs, L. Carey, A. Meretoja, S.M. Davis, and G.A. Donnan, for the EXTEND Investigators*

N ENGL J MED 380;19 NEJM.ORG MAY 9, 2019

- Imaging inclusion criteria:
  - Mismatch ratio ≥ 1.2;
  - Core volume ≤ 70 mL;
  - Mismatch volume ≥ 10 mL
- Time from stroke onset 4.5 to 9 hours
- Alteplase n = 113 vs Placebo n = 112



Favorable outcome: **Alteplase 35.4%** vs Placebo 29.5%

What does this mean for stroke care in our region?

- It means that we may be able to treat stroke patients up to 9 hours after stroke onset with either tPA or TNK if certain conditions are met:

  - If using MRI: DWI positive for infarction, FLAIR negative
  - If using CT perfusion: Ischemic penumbra is larger than infarct core
  - Patient is independent at baseline

Box 5A Time Windows for Reperfusion in Acute Ischemic Stroke

Available treatments	Time from stroke onset or last known well	Population	Notes and criteria
Screening for stroke signs and symptoms	Within 24 hours	All patients showing signs of acute disabling stroke	
Intravenous thrombolysis	0 to 4.5 hours	All patients showing signs of acute disabling stroke	Based on CT/CTA
	4.5 to 6 hours	Select patients showing signs of acute disabling stroke	Requires advanced imaging for tissue-based decision-making
	6 to 9 hours	Select patients - in discussion with a stroke expert	Requires advanced imaging for tissue-based decision-making

https://www.strokebestpractices.ca/recommendations/acute-stroke-management/acute-ischemic-stroke-treatment

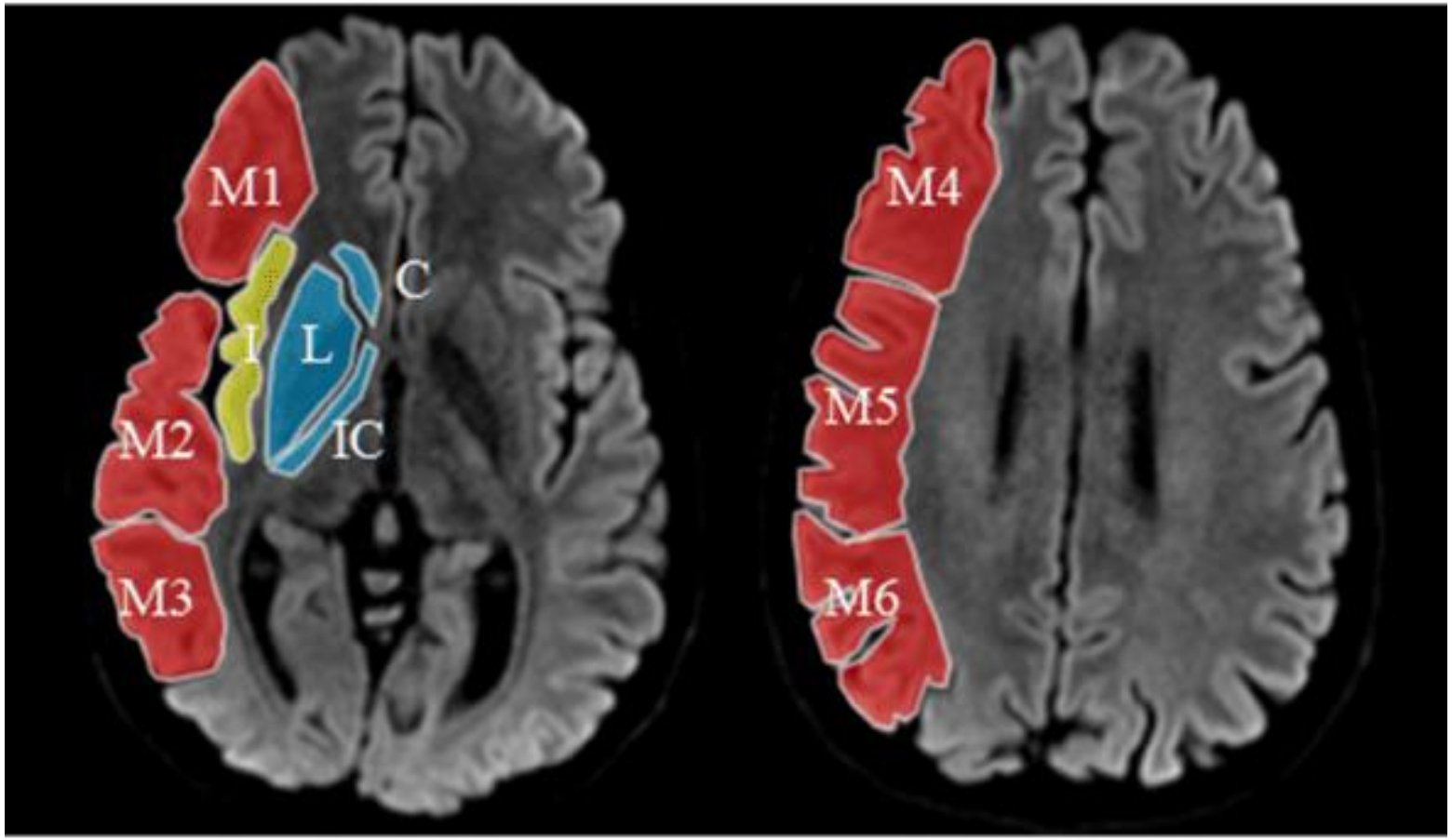
EVT for Large Strokes

- EVT has become the standard of care for large vessel occlusion, sometimes with thrombolysis

- But large strokes were excluded from clinical trials because it was felt that there was no hope of restoring function to a brain that is already badly injured

- But we have all seen large strokes where there is at least some degree of recovery

What is a large stroke?



ASPECTS

(Alberta Stroke Program Early CT Score)

10 areas: M1 to M6, C, L, IC, I

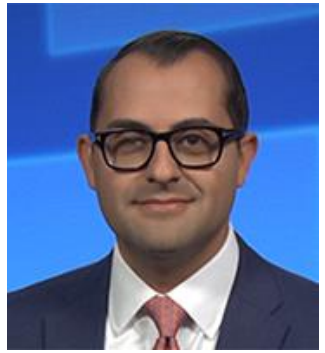
Intact brain scores 10

Complete infarction scores 0

EVT typically done for ASPECTS 6 to 10

SELECT2

- Trials of the efficacy and safety of endovascular thrombectomy in patients with large ischemic strokes have been carried out in limited populations.


ORIGINAL ARTICLE

Trial of Endovascular Thrombectomy for Large Ischemic Strokes

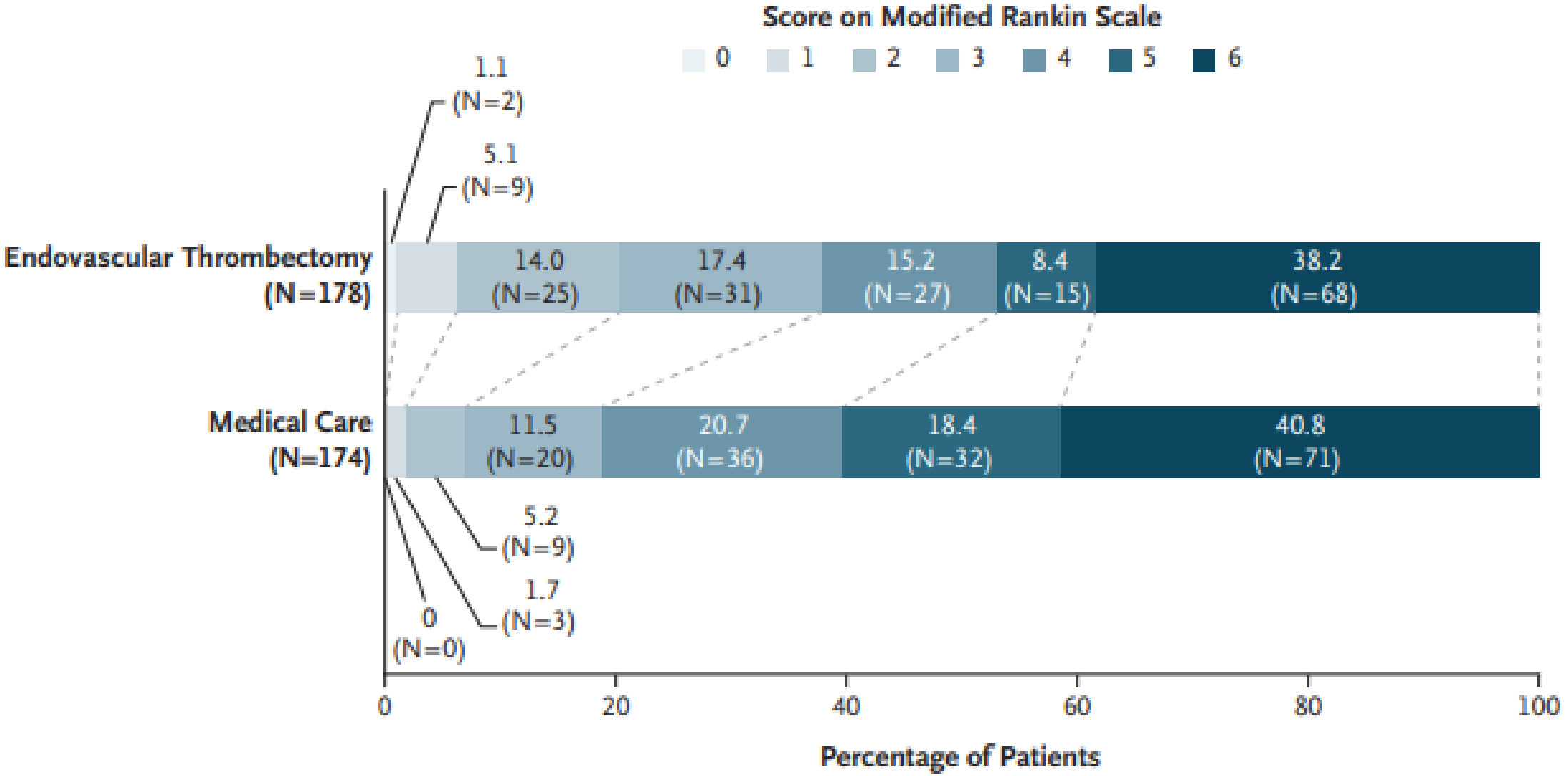
A. Sarraj, A.E. Hassan, M.G. Abraham, S. Ortega-Gutierrez, S.E. Kasner, M.S. Hussain, M. Chen, S. Blackburn, C.W. Sitton, L. Churilov, S. Sundararajan, Y.C. Hu, N.A. Herial, P. Jabbour, D. Gibson, A.N. Wallace, J.F. Arenillas, J.P. Tsai, R.F. Budzik, W.J. Hicks, O. Kozak, B. Yan, D.J. Cordato, N.W. Manning, M.W. Parsons, R.A. Hanel, A.N. Aghaebrahim, T.Y. Wu, P. Cardona-Portela, N. Pérez de la Ossa, J.D. Schaafsma, J. Blasco, N. Sangha, S. Warach, C.D. Gandhi, T.J. Kleinig, D. Sahlein, L. Elijovich, W. Tekle, E.A. Samaniego, L. Maali, M.A. Abdulrazzak, M.N. Psychogios, A. Shuaib, D.K. Pujara, F. Shaker, H. Johns, G. Sharma, V. Yogendrakumar, F.C. Ng, M.H. Rahbar, C. Cai, P. Lavori, S. Hamilton, T. Nguyen, J.T. Fifi, S. Davis, L. Wechsler, V.M. Pereira, M.G. Lansberg, M.D. Hill, J.C. Grotta, M. Ribo, B.C. Campbell, and G.W. Albers, for the SELECT2 Investigators*

SELECT2 Methodology

- Multicentre trial conducted in US, Canada, Europe, Australia, NZ
- ASPECTS 3 to 5 or infarct core volume greater than 50 mL
- Within 24 hours of stroke onset
- EVT and Medical Care vs Medical Care alone
- Primary outcome: ordinal shift in mRS at 90 days
- Safety outcome: Symptomatic ICH, Neurological worsening, Procedural complications

SELECT2 Results

- Total patients enrolled 352
  - Trial stopped early because of efficacy
- ASPECTS 4
- NIHSS 19
- Time from stroke onset to enrollment: 9 hours
- ~20% of patients in each treatment arm received tPA



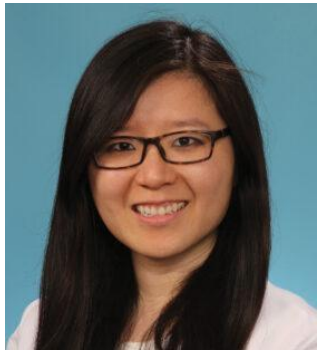
Shift in better outcomes was observed favoring EVT over Medical Care.

20% of EVT patients were independent at 90 days vs 7% with Medical Care.

ANGEL- ASPECT

- The role of endovascular therapy for acute stroke with a large infarction has not been extensively studied in differing populations.



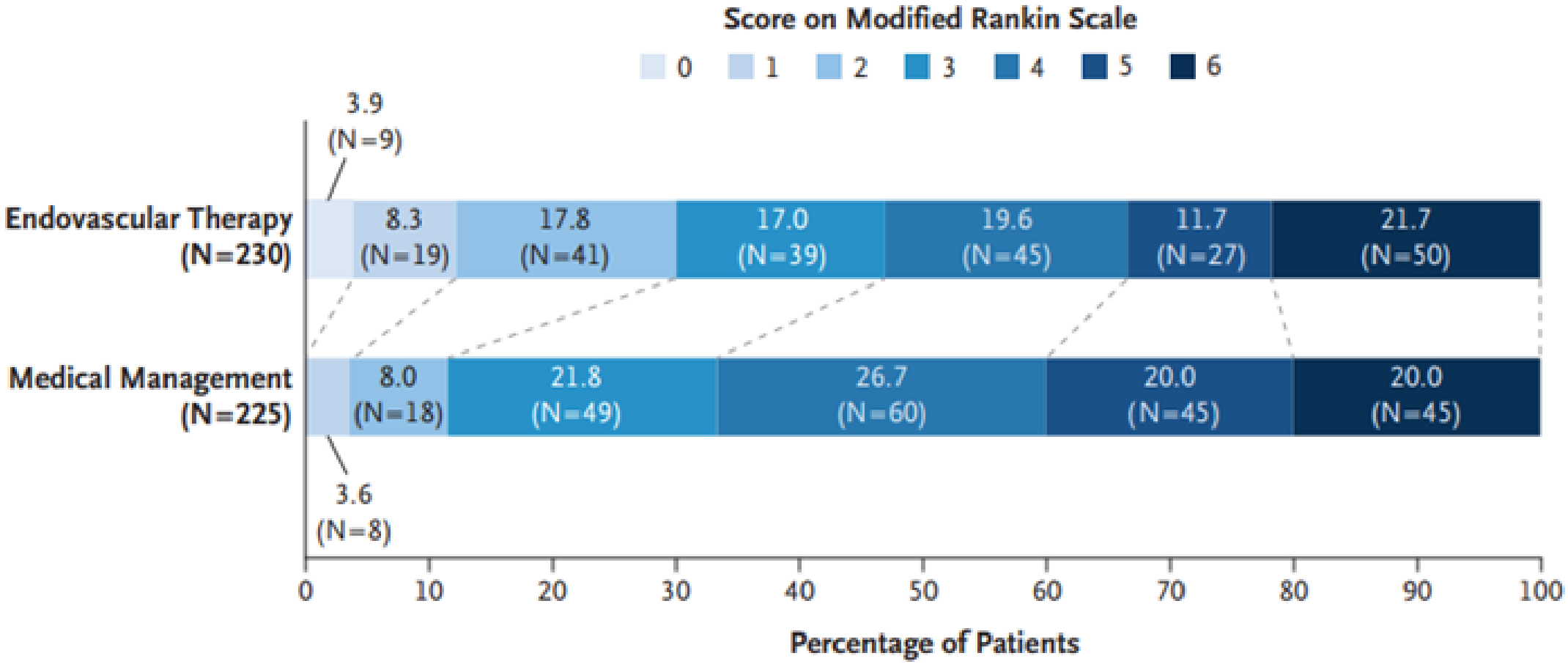


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Endovascular Therapy for Acute Ischemic Stroke with Large Infarct

uo, G. Ma, X. Tong, X. Zhang, Y. Pan, T.N. Nguyen, G. Yuan, H. Han, W. C
Wei, Jiangang Zhang, Z. Zhou, X. Yao, G. Wang, W. Song, X. Cai, G. Nan, D
.-C. Wang, W. Ling, C. Cai, C. Wen, E. Wang, L. Zhang, C. Jiang, Y. Liu, G. L
Chen, T. Li, S. Liu, J. Li, F. Gao, N. Ma, D. Mo, L. Song, X. Sun, X. Li, Y. Der
uo, M. Lv, H. He, A. Liu, Jingbo Zhang, S. Mu, Lian Liu, J. Jing, X. Nie, Z. D
Du, X. Zhao, P. Yang, Liping Liu, Yilong Wang, D.S. Liebeskind, V.M. Pere
Z. Ren, Yongjun Wang, and Z. Miao, for the ANGEL-ASPECT Investigators*



Shift in outcome favors EVT over Medical Management.

30% are independent at 90 days with EVT vs 11.6% with Medical Management.

Summing up these two recent trials…

- Risk of dying is 20% to 40% (for both EVT and Medical Care)
- With EVT chance of walking independently 38-47% vs 19-33% without EVT
- With EVT chance of functional independence 20-30% vs 7-12% without EVT
- With EVT chance of going back to almost normal is under 6%

What does this mean for stroke care in our region?

- It means that we can't use ASPECTS as a simple cut-off for deciding who should get EVT.

- The majority of patients who receive either EVT or Medical Care will be severely disabled, and it will take careful thought to decide who is likely to benefit.

- The envelope for EVT is expanding and we can expect to see the volume of EVT growing in our region.

Three Major Advances to Hyperacute Stroke Care

- TNK will eventually replace tPA everywhere and may affect how we transport patients to EVT centres.
  - ***This may expedite access to EVT in our region.***

- Thrombolysis (either tPA or TNK) can be given up to 9 hours after stroke onset in carefully selected patients.
  - ***More patients can be treated with thrombolysis.***

- EVT may be appropriate for some large strokes
  - ***More patients may benefit from EVT.***

Thank you for your attention.