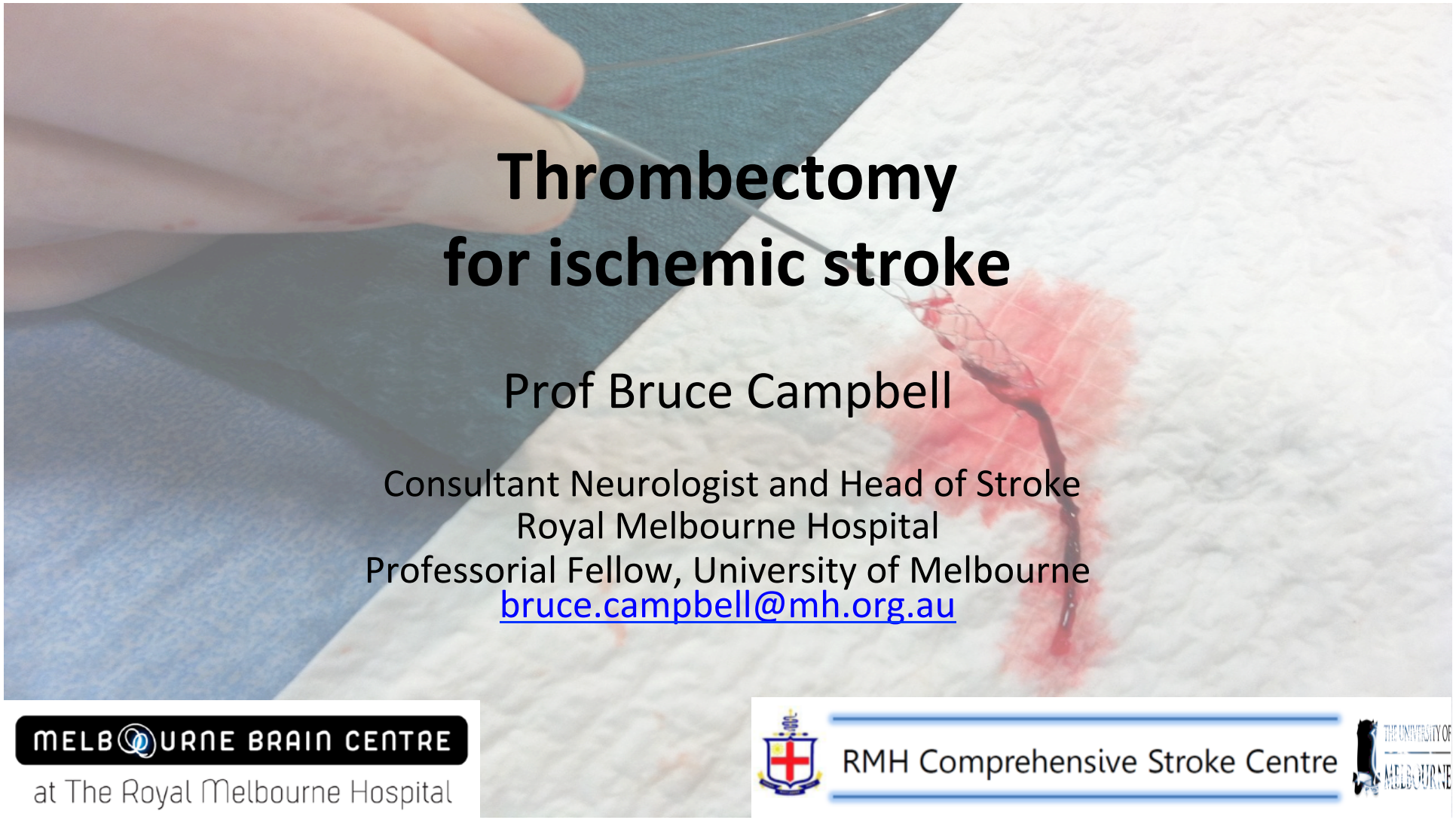

Thrombectomy for ischemic stroke

Prof Bruce Campbell

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at The Royal Melbourne Hospital

RMH Comprehensive Stroke Centre

Disclosures

- Financial disclosures − none

- Off-label use of tenecteplase for ischaemic stroke

Learning objectives

- Understand the evidence behind thrombectomy eligibility
  - site of vessel occlusion
  - age
  - severity
  - time
- Understand imaging strategies and the prognostic significance of ischemic core volume
- Understand the role of IV thrombolysis before thrombectomy
  - 0-4.5hr versus >4.5h
- Understand the critical importance of Systems of care in maximising patient outcomes

Key messages

- Endovascular thrombectomy (EVT) profoundly reduces disability in a broad range of ischemic stroke patients with large vessel occlusion 0-6h after stroke onset
- EVT also benefits selected patients with favorable perfusion imaging up to 24h after stroke onset
- Currently EVT is combined with IV thrombolysis in eligible patients (with ongoing trials testing EVT alone in patients presenting directly to EVT centers)
- Faster treatment is the most effective way to improve patient outcomes − streamline transfers and minimize re-imaging

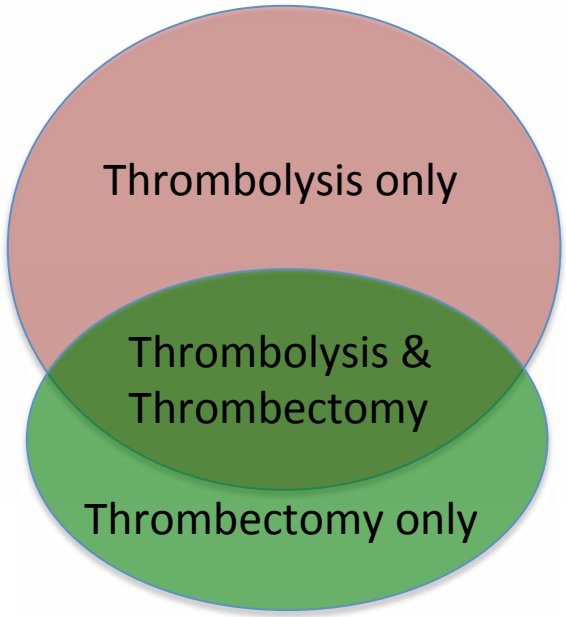
Large vessel occlusion - thrombolysis vs thrombectomy

large vessel occlusion (LVO)

- 15% of all stroke *but*
- 39% of acutely presenting stroke
- responsible for 62% of dependency and 96% of mortality (Malhotra Front Neurol 2017)
- IV thrombolysis has limited efficacy

* "LVO" definition may change with device improvements

** planned trials to add IV lysis to thrombectomy >4.5hr



>70% - no reperfusion therapy
super-mild, established, very late

EDITORIAL

Endovascular Therapy for Stroke — It's about Time

Anthony J. Furlan, M.D.

New Eng J Med 2015:

- 5 Positive randomized trials
- 2 Editorials
- Faster, better reperfusion
- More Imaging

ORIGINAL ARTICLE

A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke

O.A. Berkhemer, P.S.S. Fransen, D. Beumer, L.A. van den Berg, H.F. Lingsma, A.J. Yoo, W.J. Schonewille, J.A. Vos, P.J. Nederkoorn, M.J.H. Wermer, M.A.A. van Walderveen, J. Staals, J. Hofmeijer, J.A. van Oostayen, G.J. Lycklama à Nijeholt, J. Boiten, P.A. Brouwer, B.J. Emmer, S.F. de Bruijn, L.C. van Dijk, L.J. Kappelle, R.H. Lo, E.J. van Dijk, J. de Vries, P.L.M. de Kort, W.J.J. van Rooij, J.S.P. van den Berg, B.A.A.M. van Hasselt, L.A.M. Aerden, R.J. Dallinga, M.C. Visser, J.C.J. Bot, P.C. Vroomen, O. Eshghi, T.H.C.M.L. Schreuder, R.J.J. Heijboer, K. Keizer, A.V. Tielbeek, H.M. den Hertog, D.G. Gerrits, R.M. van den Berg-Vos, G.B. Karas, E.W. Steyerberg, H.Z. Flach, H.A. Marquering, M.E.S. Sprengers, S.F.M. Jenniskens, L.F.M. Beenen, R. van den Berg, P.J. Koudstaal, W.H. van Zwam, Y.B.W.E.M. Roos, A. van der Lugt, R.J. van Oostenbrugge, C.B.L.M. Majoie, and D.W.J. Dippel, for the MR CLEAN Investigators*

ORIGINAL ARTICLE

Stent-Retriever Thrombectomy after Intravenous t-PA vs. t-PA Alone in Stroke

Jeffrey L. Saver, M.D., Mayank Goyal, M.D., Alain Bonafe, M.D., Hans-Christoph Diener, M.D., Ph.D., Elad I. Levy, M.D., Vitor M. Pereira, M.D., Gregory W. Albers, M.D., Christophe Cognard, M.D., David J. Cohen, M.D., Werner Hacke, M.D., Ph.D., Olav Jansen, M.D., Ph.D., Tudor G. Jovin, M.D., Heinrich P. Mattle, M.D., Raul G. Nogueira, M.D., Adnan H. Siddiqui, M.D., Ph.D., Dileep R. Yavagal, M.D., Blaise W. Baxter, M.D., Thomas G. Devlin, M.D., Ph.D., Demetrius K. Lopes, M.D., Vivek K. Reddy, M.D., Richard du Mesnil de Rochemont, M.D., Oliver C. Singer, M.D., and Reza Jahan, M.D., for the SWIFT PRIME Investigators*

ORIGINAL ARTICLE

Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke

T.G. Jovin, A. Chamorro, E. Cobo, M.A. de Miquel, C.A. Molina, A. Rovira, L. San Román, J. Serena, S. Abilleira, M. Ribó, M. Millán, X. Urra, P. Cardona, E. López-Cancio, A. Tomasello, C. Castaño, J. Blasco, L. Aja, L. Dorado, H. Quesada, M. Rubiera, M. Hernández-Pérez, M. Goyal, A.M. Demchuk, R. von Kummer, M. Gallofré, and A. Dávalos, for the REVASCAT Trial Investigators*

ORIGINAL ARTICLE

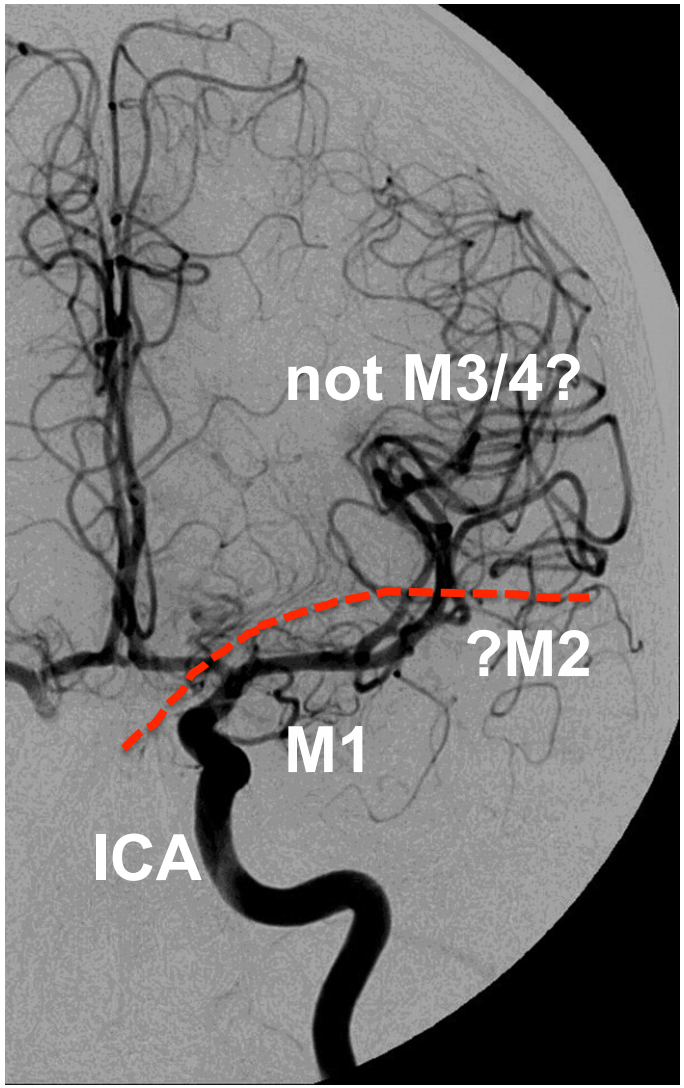
Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke

M. Goyal, A.M. Demchuk, B.K. Menon, M. Eesa, J.L. Rempel, J. Thornton, D. Roy, T.G. Jovin, R.A. Willinsky, B.L. Sapkota, D. Dowlatshahi, D.F. Frei, N.R. Kamal, W.J. Montanera, A.Y. Poppe, K.J. Ryckborst, F.L. Silver, A. Shuaib, D. Tampieri, D. Williams, O.Y. Bang, B.W. Baxter, P.A. Burns, H. Choe, J.-H. Heo, C.A. Holmstedt, B. Jankowitz, M. Kelly, G. Linares, J.L. Mandzia, J. Shankar, S.-I. Sohn, R.H. Swartz, P.A. Barber, S.B. Coutts, E.E. Smith, W.F. Morrish, A. Weill, S. Subramaniam, A.P. Mitha, J.H. Wong, M.W. Lowerison, T.T. Sajobi, and M.D. Hill for the ESCAPE Trial Investigators*

ORIGINAL ARTICLE

Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection

B.C.V. Campbell, P.J. Mitchell, T.J. Kleinig, H.M. Dewey, L. Churilov, N. Yassi, B. Yan, R.J. Dowling, M.W. Parsons, T.J. Oxley, T.Y. Wu, M. Brooks, M.A. Simpson, F. Miteff, C.R. Levi, M. Krause, T.J. Harrington, K.C. Faulder, B.S. Steinfort, M. Priglinger, T. Ang, R. Scroop, P.A. Barber, B. McGuinness, T. Wijeratne, T.G. Phan, W. Chong, R.V. Chandra, C.F. Bladin, M. Badve, H. Rice, L. de Villiers, H. Ma, P.M. Desmond, G.A. Donnan, and S.M. Davis, for the EXTEND-IA Investigators*



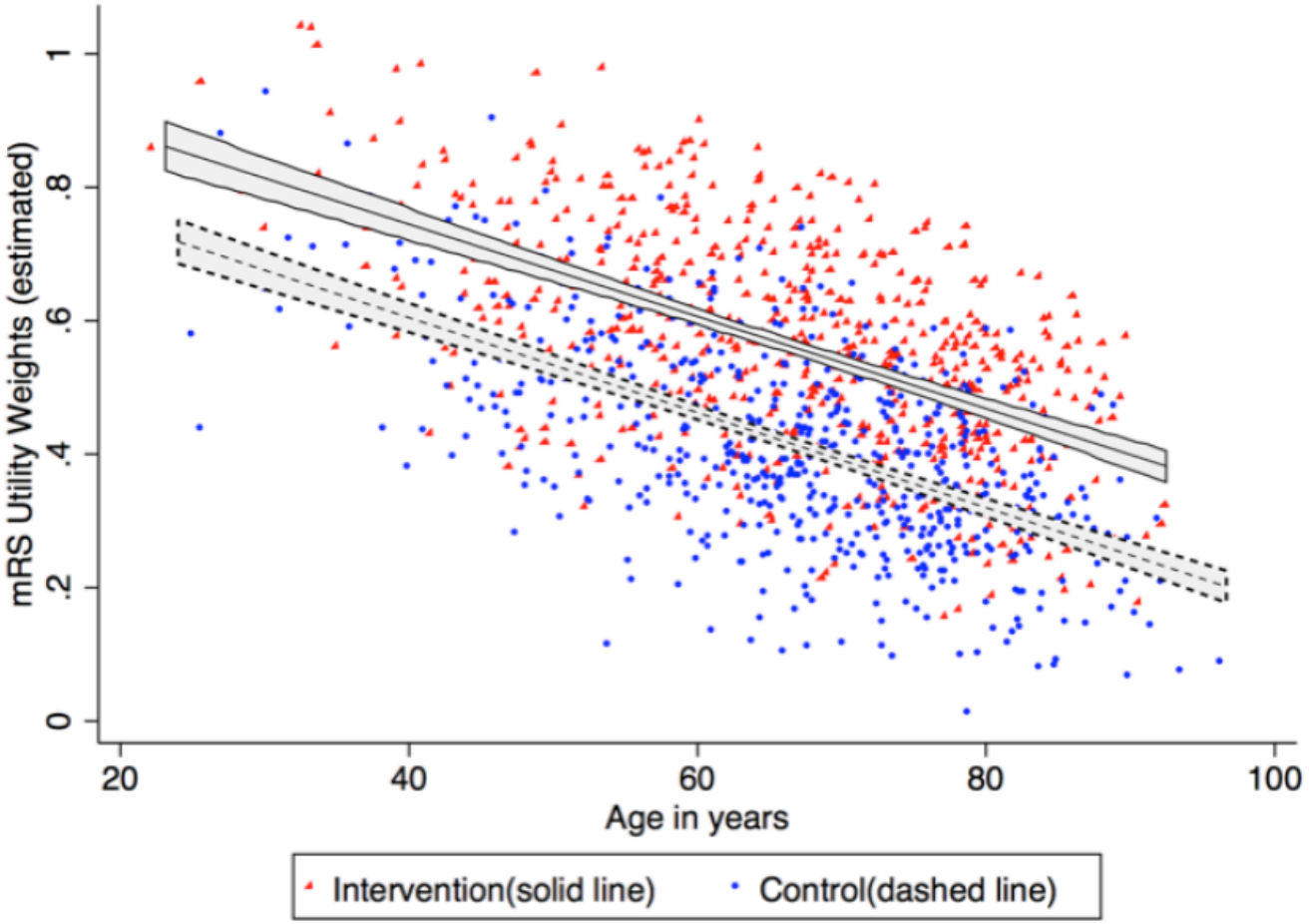
Which sites of vessel occlusion?

- **ICA and M1 – benefit**
- **tandem disease (cervical + intracranial) – benefit**
- **?M2**
  - less common, highly variable anatomy
  - smaller, more tortuous, less accessible
  - less territory at risk
  - greater response to IV thrombolysis
  - HERMES meta-analysis = larger/dominant/more proximal M2 with higher NIHSS benefit − need to individualize decision
- **M3/4, ACA, PCA - ??**
- **Basilar** – excluded from most trials, BEST 20% benefit "as treated", BASICS RCT ongoing. time window: ?24hr from last known well vs ~8hr from onset of coma

Age limits?

Age is prognostic

Age **does not** modify treatment effect



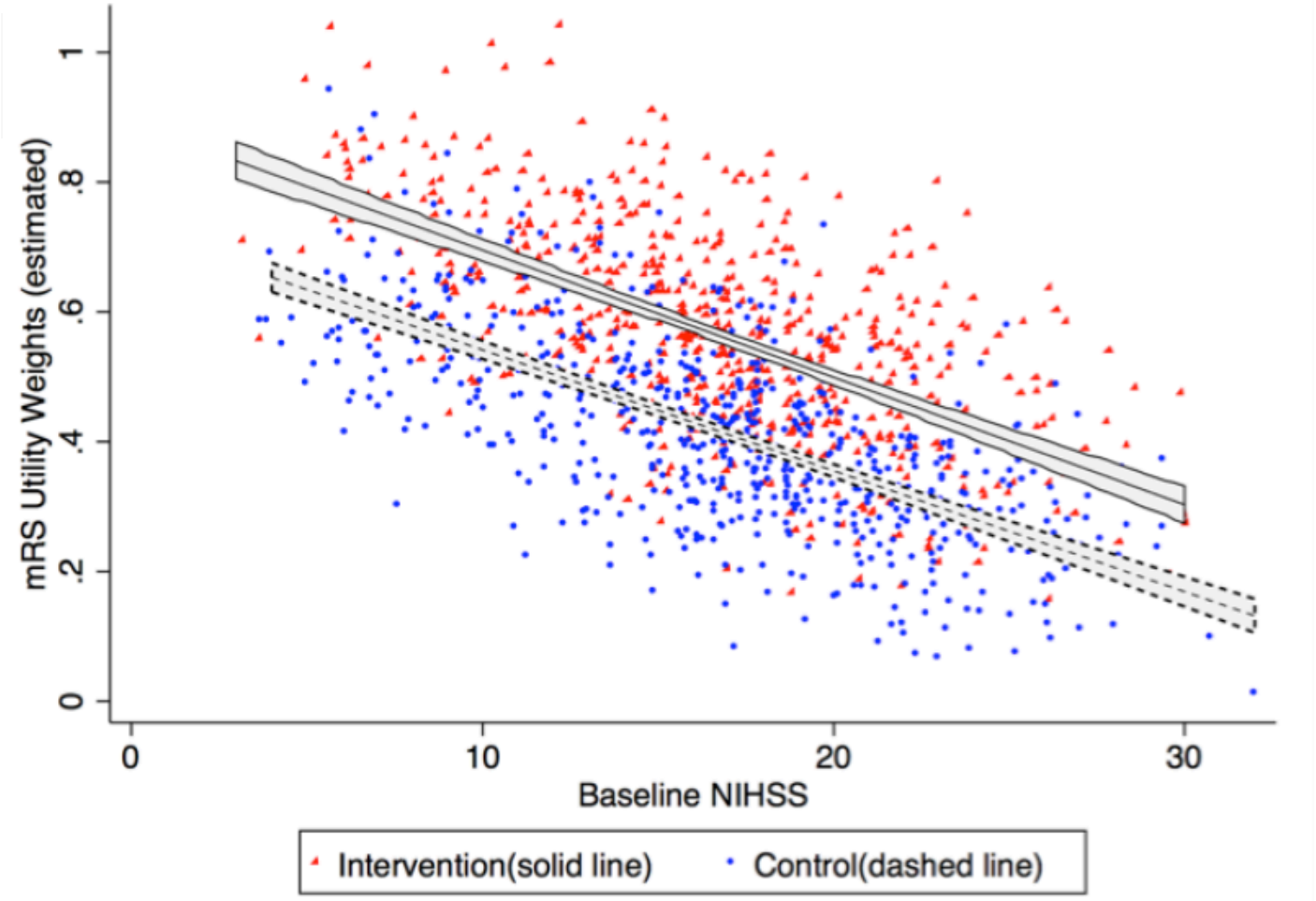
Goyal et al Lancet 2016

Severity limits?

NIHSS is prognostic

NIHSS **does not** modify treatment effect

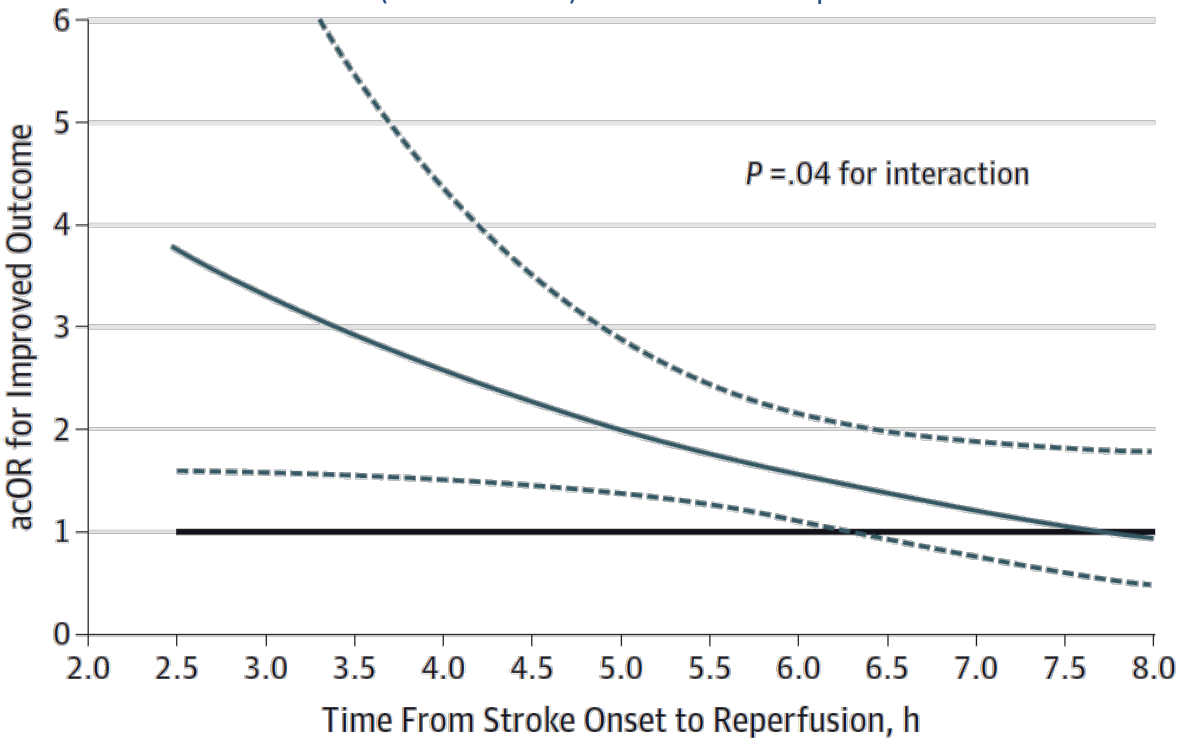
Uncertainty in very mild (NIHSS 0-5)
→ ENDO LOW trial



Goyal et al Lancet 2016

Thrombectomy – still time critical

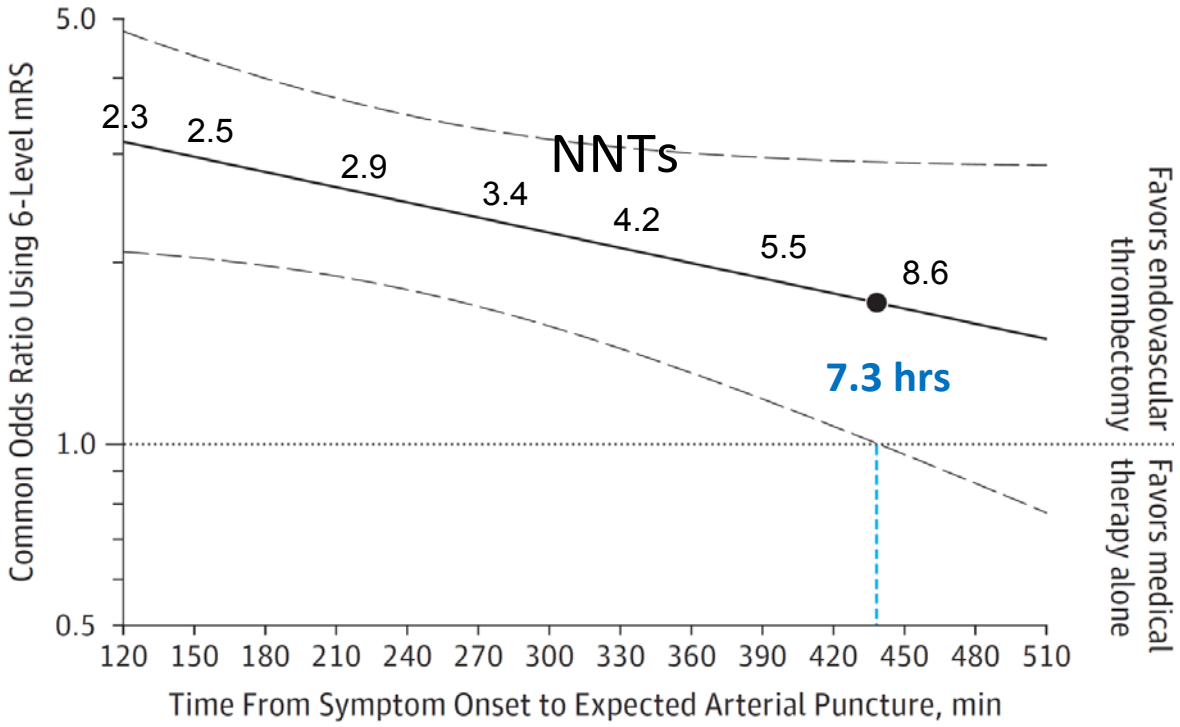
MR CLEAN selection (CTA occlusion) with successful reperfusion



Fransen JAMA Neurology 2016

Thrombectomy – still time critical

For every 4 min delay
after reaching emergency
1 in 100 patients will have
increased disability



Saver JAMA 2016

ORIGINAL ARTICLE

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

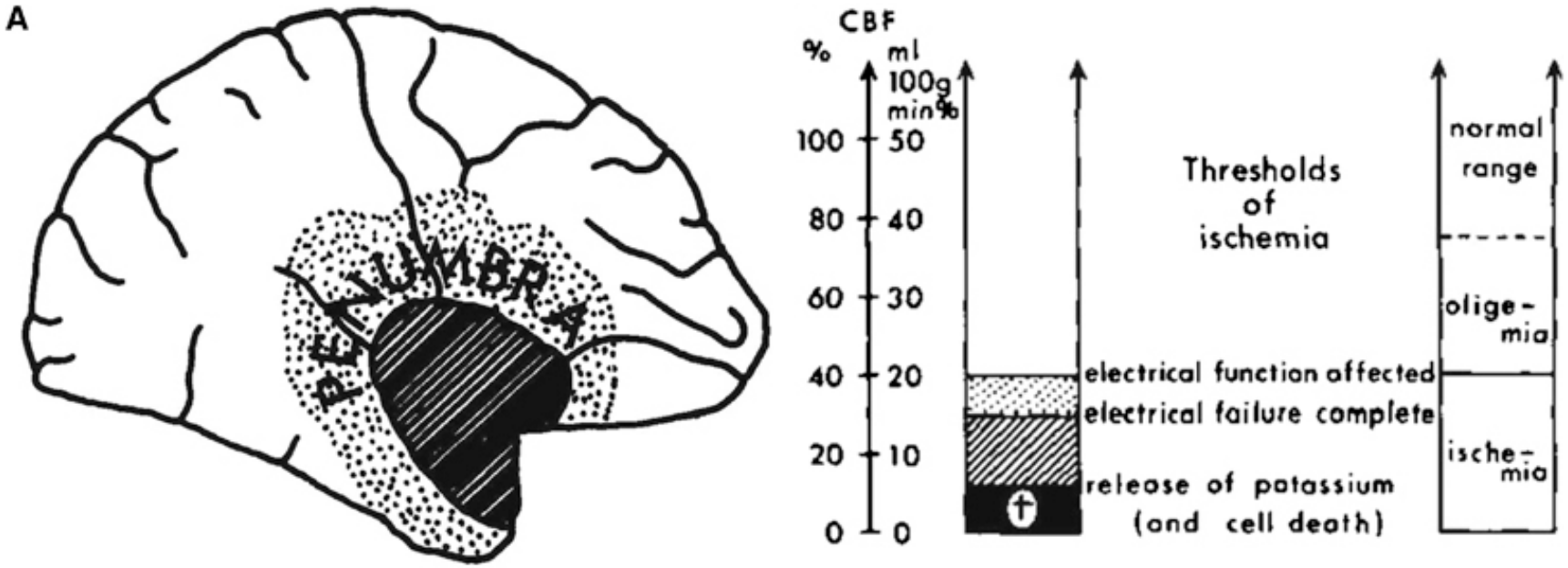
R.G. Nogueira, A.P. Jadhav, D.C. Haussen, A. Bonafe, R.F. Budzik, P. Bhuva, D.R. Yavagal, M. Ribo, C. Cognard, R.A. Hanel, C.A. Sila, A.E. Hassan, M. Millan, E.I. Levy, P. Mitchell, M. Chen, J.D. English, Q.A. Shah, F.L. Silver, V.M. Pereira, B.P. Mehta, B.W. Baxter, M.G. Abraham, P. Cardona, E. Veznedaroglu, 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*

ORIGINAL ARTICLE

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

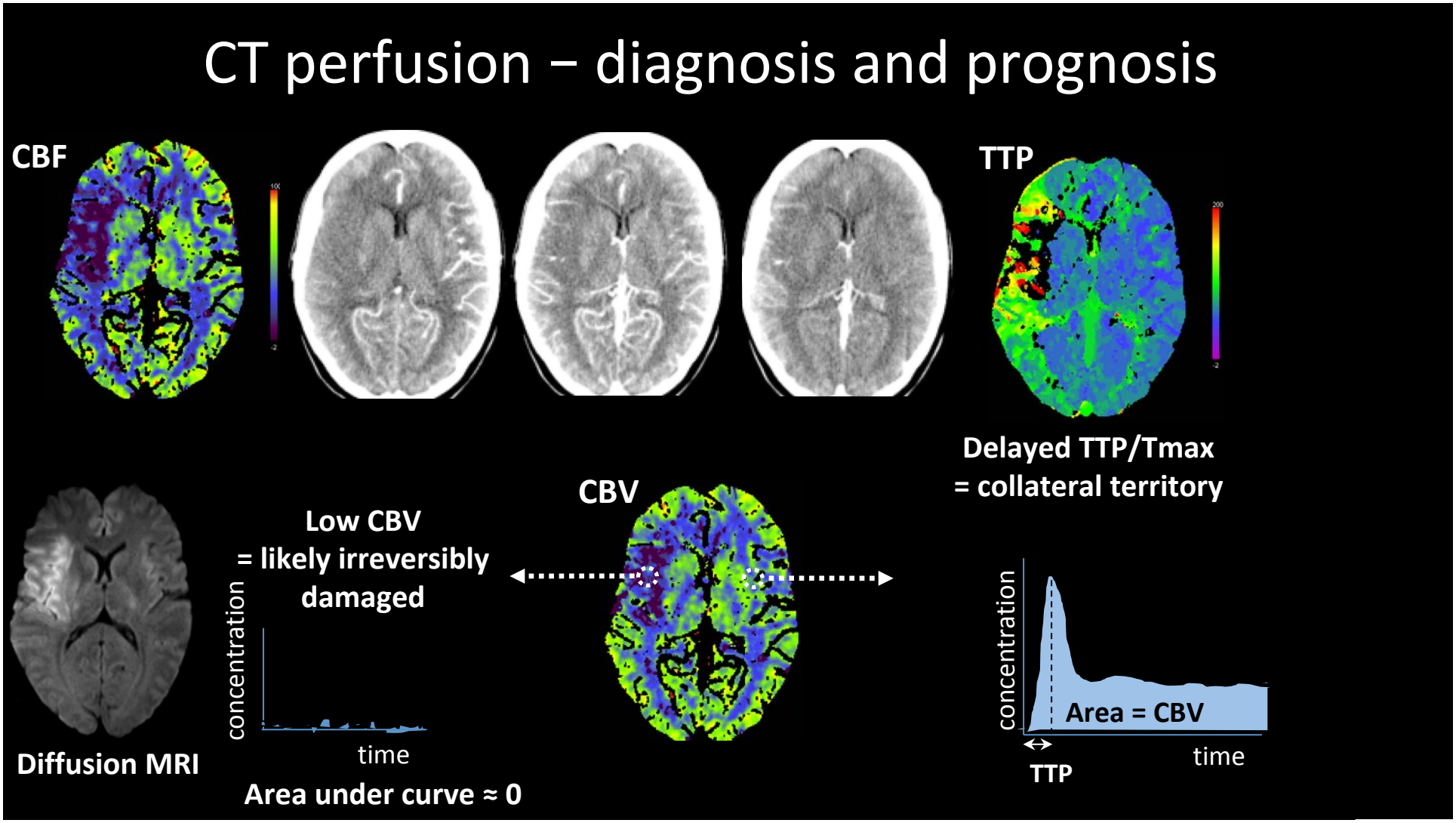
G.W. Albers, M.P. Marks, S. Kemp, S. Christensen, J.P. Tsai, S. Ortega-Gutierrez, R.A. McTaggart, M.T. Torbey, M. Kim-Tenser, T. Leslie-Mazwi, A. Sarraj, S.E. Kasner, S.A. Ansari, S.D. Yeatts, S. Hamilton, M. Mlynash, J.J. Heit, G. Zaharchuk, S. Kim, J. Carrozzella, Y.Y. Palesch, A.M. Demchuk, R. Bammer,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

Ischemic Penumbra – the reason we can improve outcome after ischaemic stroke

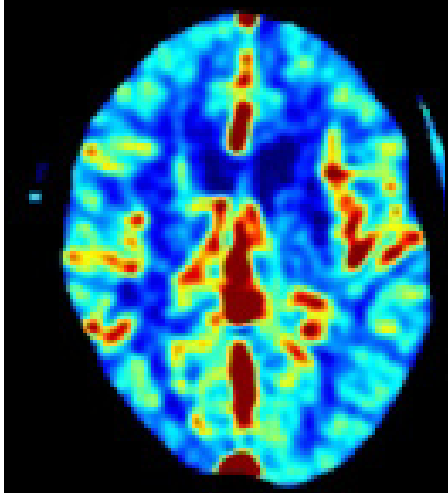


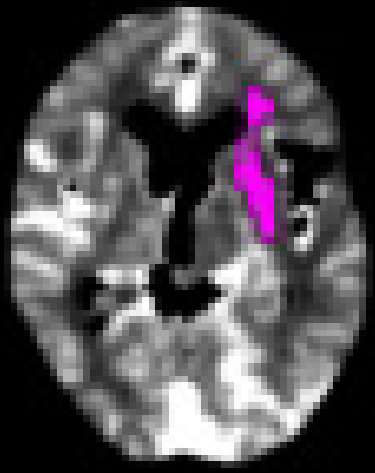
Astrup, Symon 1977

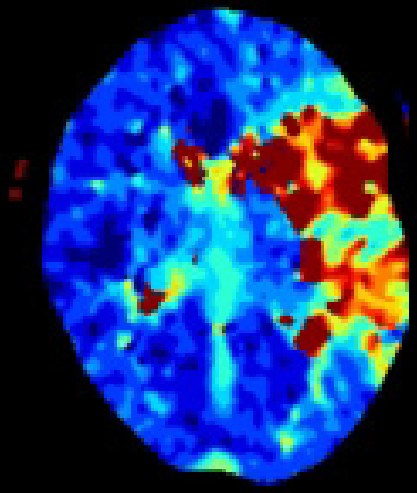
CT perfusion – diagnosis and prognosis

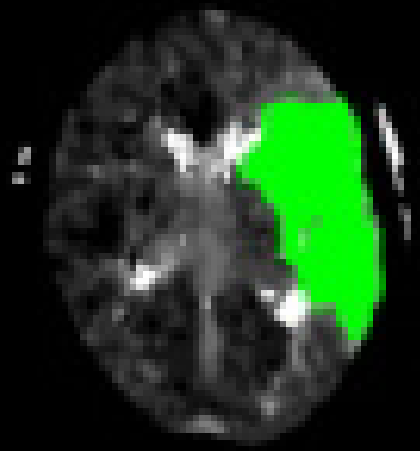


Automated CT perfusion processing









"How much blood supply"
(severely reduced ≈ dead)

relCBF<30% of normal brain Campbell et al Stroke 2011
* time to reperf & grey vs white matter

"How delayed is the blood supply"
(severely delayed ≈ at risk)

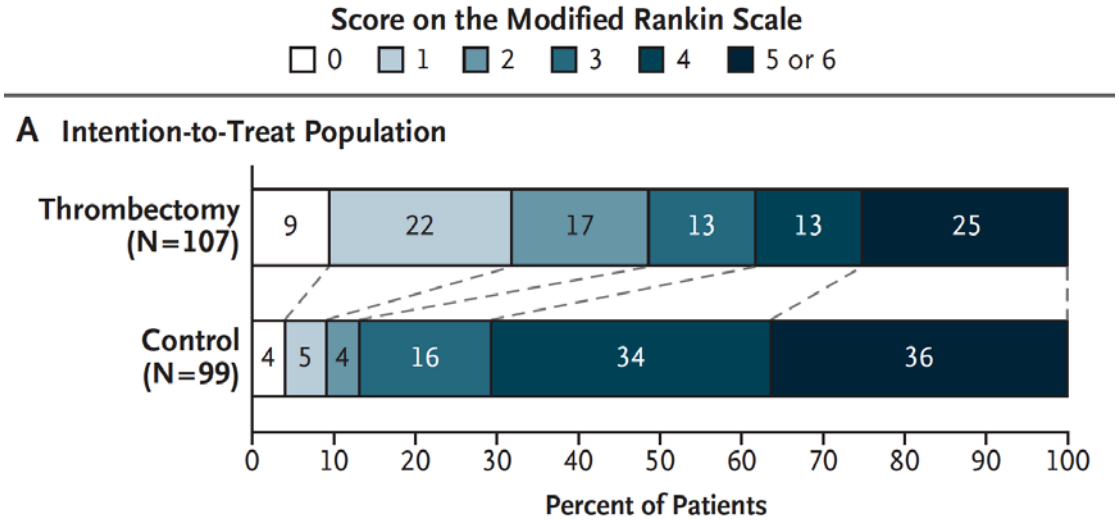
iSchemaView RAPID
version 4.7

ordinal NNT 2.0

mRS 0-2: 49% vs 13%, p<0.0001

84% mTICI 2b/3

SICH 5.6% vs 3.0%, p=0.50



Nogueira NEJM 2017

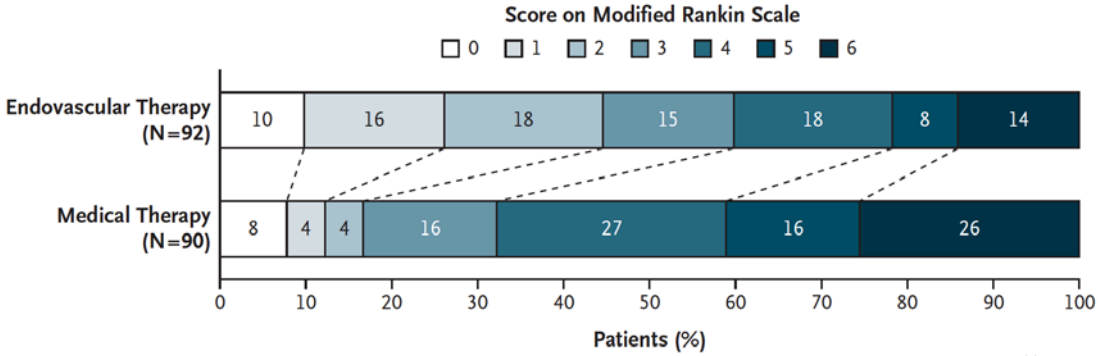
defuse·3

ordinal NNT 2.1

mRS 0-2 45% vs 17%, p<0.0001

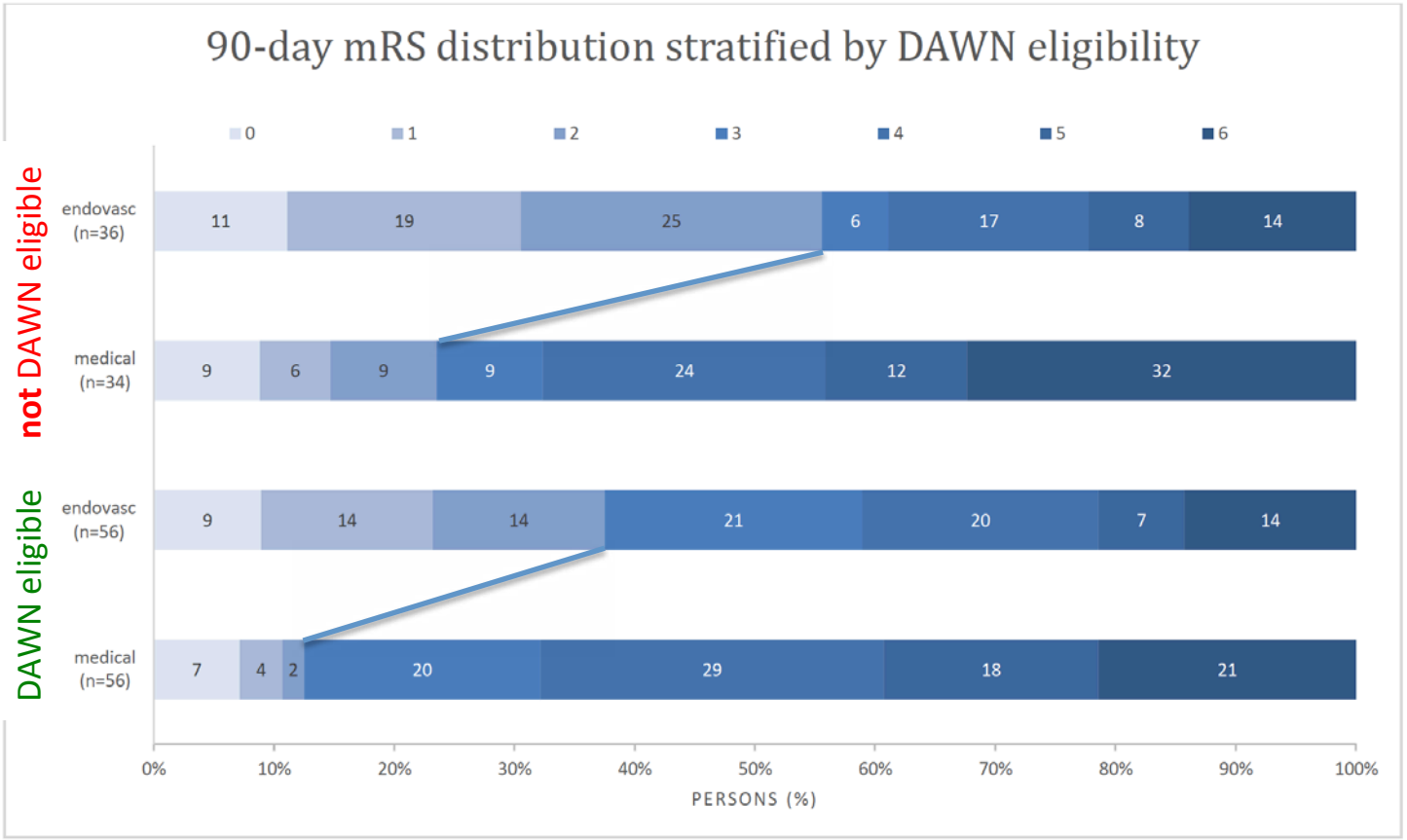
76% mTICI 2b/3

SICH 6.5% vs 4.4%, p=0.75



Albers NEJM 2018

DAWN eligibility effect in DEFUSE 3



DAWN Ineligible, (OR 2.96, 95% CI 1.26-6.97); DAWN Eligible, (OR 2.66, 95% CI 1.36-5.23) P value for interaction = 0.47

DEFUSE 3 criteria

- simpler
- ~60% more patients eligible
- No reduction in treatment effect within age, NIHSS or core volumes included

i.e. 6-24hr with ICA/M1 and <70mL core → thrombectomy

Albers et al NEJM 2018

Is time still brain? **Yes!**

- Overall stroke population are very time sensitive – still need to go as fast as possible
- The proportion of patients who remain eligible by imaging criteria decreases over time (~50% of LVO in the 6-24hr time window based on DEFUSE 3 screening)
- However, if an individual patient is unavoidably delayed in presentation AND imaging is still favorable then they are likely to benefit from reperfusion

advanced imaging is not just about “excluding” patients

- including more patients
  - mild NIHSS but significant perfusion abnormality
  - late/unknown time
  - “low ASPECTS” but only moderate volume NCCT changes
  - clinically “marginal” but good imaging

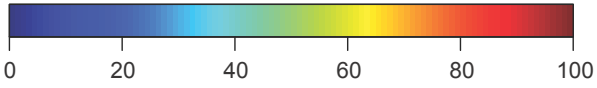
AND

- diagnostic benefits
  - when patients present the first question is “is it stroke”
  - variable levels of experience on ground, in-hours, after-hours, telemedicine
  - improved NCCT interpretation when you know where to scrutinize
  - LVO may be chronic, partial, asymptomatic − perfusion can help

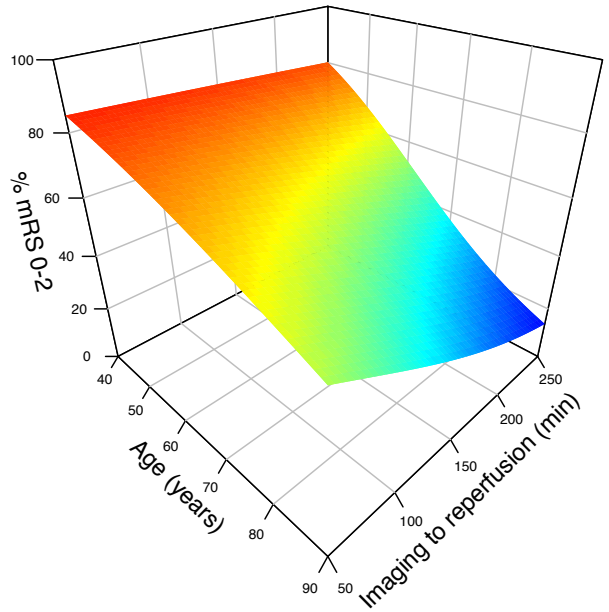
AND

- Maybe in future we will have non-reperfusion-based therapies…
  - glyburide, NA1 etc might benefit from imaging to target those not likely to do well just with reperfusion

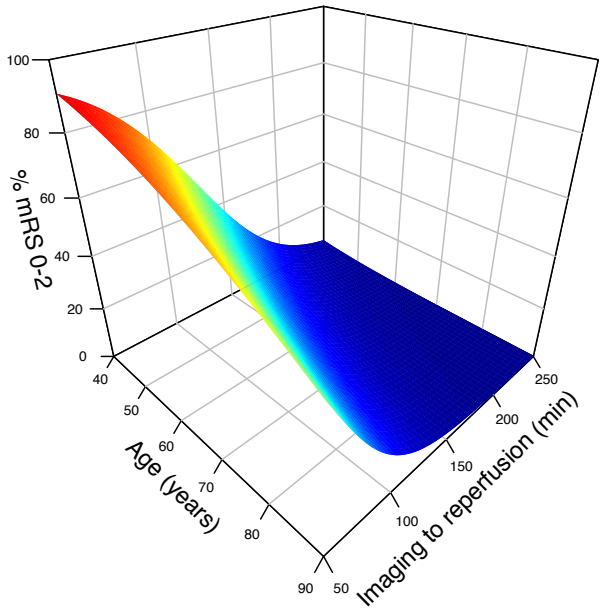
Impact of **Core volume**, **Age** and **Time (imaging to reperfusion)** on functional outcome in patients successfully reperfused



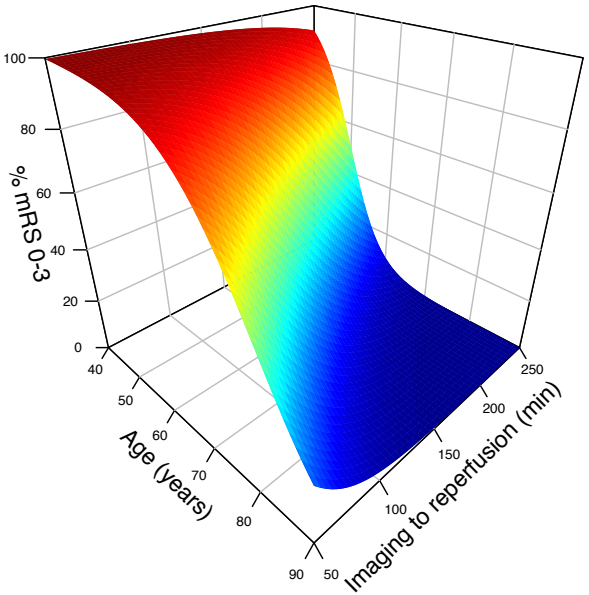
10ml core mRS 0-2



100mL core mRS 0-2



100mL core mRS 0-3



For 0-6 hour patients don't exclude purely on basis of core volume:

Balance core volume and location,
expected time to reperfusion,
pre-morbid status & tolerance of disability if known

Campbell et al Lancet Neurology 2019

If eligible for both treatments should we still give thrombolysis before thrombectomy?

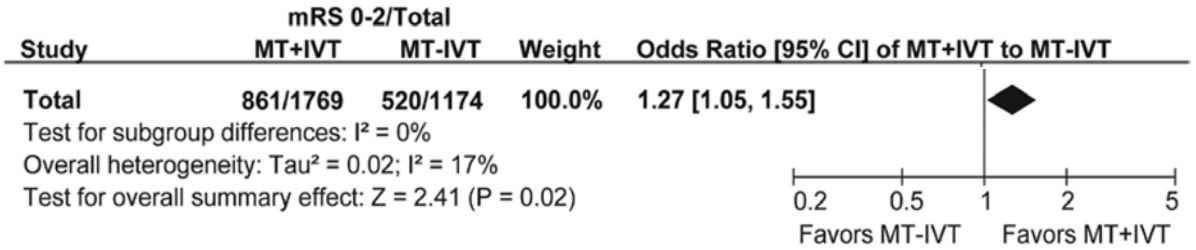
	Intervention	Alteplase	Standard care
Final Reperfusion TICI 2b/3 [Angio Core lab determined]	77%	---	---
mAOL 2-3 (at 2-8h CTA) [CT Core lab determined]	---	37%	7%

Goyal et al ESCAPE, NEJM 2015

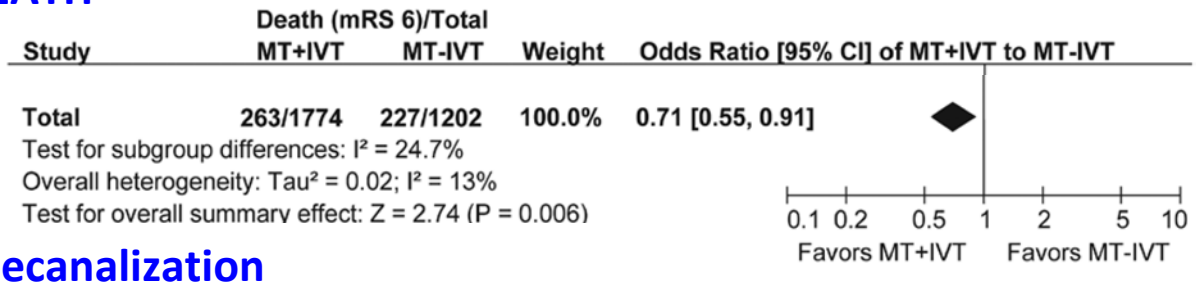
IV-IA bridging	Direct IA
potential benefit if failure/delay in endovascular procedure	potential reduction in symptomatic intracerebral (and systemic) hemorrhage
potential benefit in dissolving distal embolic fragments of thrombus/multi-territory emboli	potential reduction in distal migration/fragmentation of thrombus “out of reach” prior to endovascular procedure
potential for pre-endovascular reperfusion	save cost of alteplase/tenecteplase

Meta-analysis of observational data

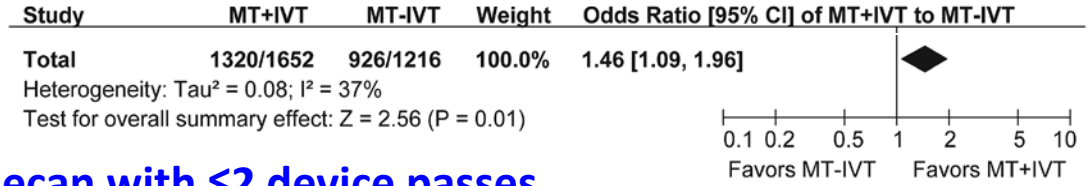
mRS 0-2



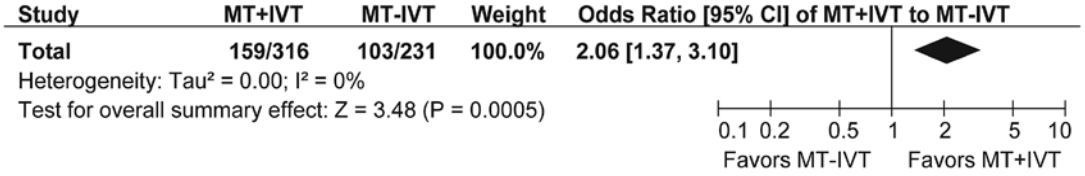
DEATH



Recanalization



Recan with ≤2 device passes



NB mostly “direct” patients were lysis-ineligible

patients intended for thrombectomy who recanalize prior were not included…

?thrombolysis facilitates thrombectomy
even if reperfusion not achieved prior to procedure

Mistry Stroke 2017

Systems of Care – Time is Brain!

Conclusions

Rapid reperfusion remains the proven treatment paradigm in stroke

- Currently thrombolysis + thrombectomy if eligible for both (DIRECT trials ongoing)
- Thrombectomy for ICA, M1, tandem, basilar, selected M2 occlusions
- “Good” premorbid function
- No age or clinical severity limits
- **0-6h:** broad imaging criteria **6-24h:** DEFUSE 3 imaging selection <70mL core
- CT perfusion is diagnostic and characterizes irreversibly injured core/collaterals - very helpful for prognosis in any time window
- Simply delivering thrombolysis & thrombectomy faster and increasing access to appropriate patients is essential to maximize effectiveness − focus on systems of care

~