Stroke

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Major clinical trials in stroke – year 2020

- LDL target after AIS – ***TST trial***
- Ticagrelor + Aspirin combination therapy in early stroke period – ***THALES trial***
- rtPA before EVT – ***DIRECT-MT, SKIP, DEVT trial***
- Nerinetide for AIS – ***ESCAPE-NA1 trial***


2020 Round-up

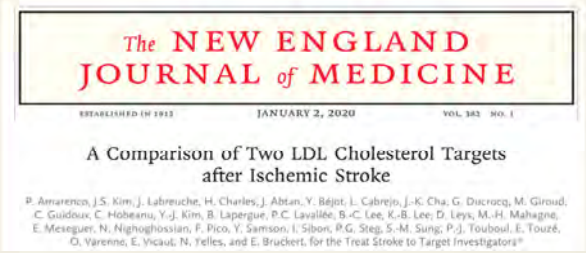
Important advances in stroke research in 2020

Lancet Neurol. 2021 Jan;20(1):2-3.

Treat Stroke to Target (TST) trial

✓ High-intensity statin for atherosclerotic ischemic stroke
- SPARCL trial N Engl J Med 2006; 355:549-559

✓ No specified target LDL level for atherosclerotic stroke in the current guideline


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 2, 2020 VOL. 382 NO. 1

A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke

P. Amarenco, J.S. Kim, J. Labreuche, H. Charles, J. Abtan, Y. Béjot, L. Cabrejo, J.-K. Cha, G. Ducrocq, M. Giroud, C. Guidoux, C. Hobeanu, Y.-J. Kim, B. Lapergue, P.C. Lavallée, B.-C. Lee, K.-B. Lee, D. Leys, M.-H. Mahagne, E. Meseguer, N. Nighoghossian, F. Pico, Y. Samson, I. Sibon, P.G. Steg, S.-M. Sung, P.-J. Touboul, E. Touzé, O. Varenne, E. Vicaut, N. Yelles, and E. Bruckert, for the Treat Stroke to Target Investigators*

Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin and an LDL-C level ≥100 mg/dL with or without evidence for other clinical ASCVD *(Class I; Level of Evidence B)*.

Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin, an LDL-C level <100 mg/dL, and no evidence for other clinical ASCVD *(Class I; Level of Evidence C)*.

2014 AHA/ASA Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack

Treat Stroke to Target (TST) trial

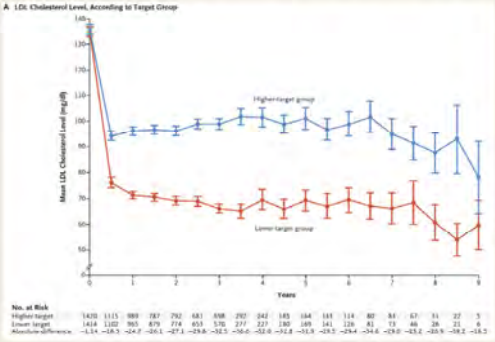
✓ Korean & French patients
- Korean patients were enrolled later in the trial

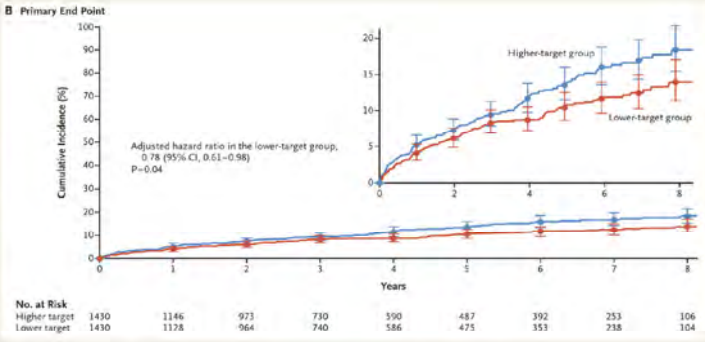
✓ **Eligibility criteria**
- Ischemic stroke within 3 months (TIA within 2 weeks)
- mRS 0-3
- Atherosclerotic stroke: ipsilateral or contralateral stenosis of intra/extracerebral artery at least 4mm plaque of the aortic arch
- Indication for statin treatment: ≥70mg/dL for statin users and ≥100mg/dL for statin non-users

✓ LDL target 70mg/dL vs. 100mg/dL

✓ **Primary efficacy outcome**: composite of major cerebrovascular events

Treat Stroke to Target (TST) trial





N = 2,860, median f/u: 3.5yrs

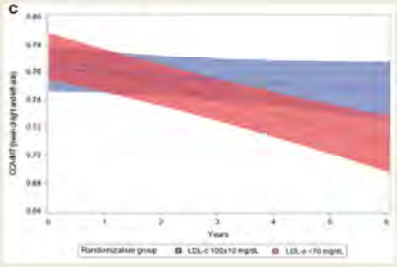
Primary efficacy outcome: 8.5% vs. 10.9%

Intracerebral hemorrhage: 1.3% vs. 0.9%, aHR 1.38 (0.68-2.82)
Newly diagnosed diabetes: 7.2% vs. 5.7%, aHR 1.27 (0.95-1.70)

Country				
France	103/1073	139/1075		0.73 (0.57–0.95)
South Korea	18/357	17/355		1.11 (0.57–2.15)

→ Ongoing f/u for Koreans

TST-PLUS



ORIGINAL RESEARCH ARTICLE

Carotid Atherosclerosis Evolution When Targeting a Low-Density Lipoprotein Cholesterol Concentration <70 mg/dL After an Ischemic Stroke of Atherosclerotic Origin

Circulation. 2020;142:748–757.

	LDL-C <70 mg/dL (n=201)	LDL-C 100±10 mg/dL (n=212)	Effect Size, HR (95% CI) or Difference	*P* Value
Primary outcome: new plaque on carotid bifurcation or internal carotid artery, n/n (5-year rate, %)	46/201 (22.9)	45/212 (21.2)		
Unadjusted analysis			1.03 (0.68 to 1.56)	0.88
Adjusted analysis*			1.01 (0.66 to 1.53)	0.98
Secondary outcome: Change in CCA-IMT, μm/y (95% CI)†				
Unadjusted analysis	−10.53 (−14.21 to −6.85)	−2.69 (−6.55 to 1.18)	−7.84 (−13.18 to −2.51)	0.004
Adjusted analysis*	−10.45 (−14.15 to −6.74)	−2.08 (−5.97 to 1.82)	−8.37 (−13.74 to −2.99)	0.002

✓ No difference in the 3-year rate of new plaque occurrence
✓ Further improved regression of carotid atherosclerosis as measured by common carotid artery IMT

THALES trial

✓ Efficacy of aspirin & clopidogrel combination therapy in patients with minor stroke or high-risk TIA

CHANCE, 2013

Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack

Yongjun Wang, M.D., Yilong Wang, M.D., Ph.D., Xingquan Zhao, M.D., Ph.D., Liping Liu, M.D., Ph.D., David Wang, D.O., F.A.H.A., F.A.A.N., Chunxue Wang, M.D., Ph.D., Chen Wang, M.D., Hao Li, Ph.D., Xia Meng, M.D., Ph.D., Liyng Cui, M.D., Ph.D., Jianping Jia, M.D., Ph.D., Qiang Dong, M.D., Ph.D., Anding Xu, M.D., Ph.D., Jinsheng Zeng, M.D., Ph.D., Yansheng Li, M.D., Ph.D., Zhimin Wang, M.D., Haiqin Xia, M.D., and S. Claiborne Johnston, M.D., Ph.D., for the CHANCE Investigators*

POINT, 2018

Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA

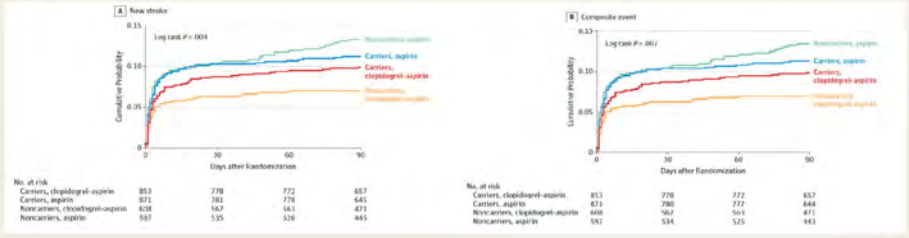
S. Claiborne Johnston, M.D., Ph.D., J. Donald Easton, M.D., Mary Farrant, M.B.A., William Barsan, M.D., Robin A. Conwit, M.D., Jordan J. Elm, Ph.D., Anthony S. Kim, M.D., Anne S. Lindblad, Ph.D., and Yuko Y. Palesch, Ph.D., for the Clinical Research Collaboration, Neurological Emergencies Treatment Trials Network, and the POINT Investigators*

In patients presenting with minor noncardioembolic ischemic stroke (NIHSS score ≤3) who did not receive IV alteplase, treatment with dual antiplatelet therapy (aspirin and clopidogrel) started within 24 hours after symptom onset and continued for 21 days is effective in reducing recurrent ischemic stroke for a period of up to 90 days from symptom onset.

AHA/ASA Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke

CYP2C19 loss-of-function allele status and efficacy of clopidogrel

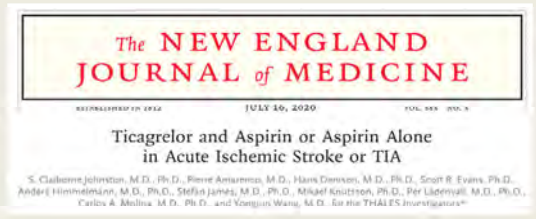
	Carriers[a] No. (%)					Noncarriers[b] No. (%)					
Outcome	Total (n = 1726)	Aspirin (n = 872)	Clopidogrel-Aspirin (n = 854)	Hazard Ratio (95% CI)	P Value	Total (n = 1207)	Aspirin (n = 598)	Clopidogrel-Aspirin (n = 609)	Hazard Ratio (95% CI)	P Value	P Value for Interaction
Stroke	174 (10.1)	94 (10.8)	80 (9.4)	0.93 (0.69-1.26)	.64	115 (9.5)	74 (12.4)	41 (6.7)	0.51 (0.35-0.75)	<.01	.02
Composite event[c]	175 (10.1)	95 (10.9)	80 (9.4)	0.92 (0.68-1.24)	.59	116 (9.6)	75 (12.5)	41 (6.7)	0.50 (0.34-0.74)	<.01	.02
Ischemic stroke	171 (9.9)	93 (10.7)	78 (9.1)	0.85 (0.63-1.15)	.29	113 (9.4)	74 (12.4)	39 (6.4)	0.51 (0.34-0.75)	<.01	.03
Bleeding[d]											
Severe	1 (0.1)	0 (0.0)	1 (0.1)	NE		1 (0.1)	1 (0.2)	0 (0.0)	NE		
Moderate	2 (0.1)	0 (0.0)	2 (0.2)	NE		0 (0.0)	0 (0.0)	0 (0.0)	NE		
Mild	10 (0.6)	2 (0.2)	8 (0.9)	4.05 (0.86-19.05)	.08	16 (1.3)	7 (1.2)	9 (1.5)	1.23 (0.46-3.29)	.69	.20
Any bleeding	32 (1.9)	12 (1.4)	20 (2.3)	1.65 (0.80-3.40)	.17	25 (2.1)	10 (1.7)	15 (2.5)	1.42 (0.64-3.15)	.39	.78



JAMA. 2016;316(1):70-78.

THALES trial

Acute STroke or Transient IscHaemic Attack Treated With TicAgre Lor and ASA for PrEvention of Stroke and Death (THALES)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JULY 16, 2020

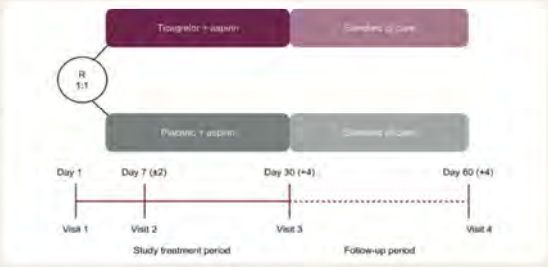
Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA

S. Claiborne Johnston, M.D., Ph.D., Pierre Amarenco, M.D., Hans Denison, M.D., Ph.D., Scott R. Evans, Ph.D., Anders Himmelmann, M.D., Ph.D., Stefan James, M.D., Ph.D., Mikael Knutsson, Ph.D., Per Ladenvall, M.D., Ph.D., Carlos A. Molina, M.D., Ph.D., and Yongjun Wang, M.D., for the THALES Investigators*

Subject : TIA or minor acute ischemic stroke

1. NIHSS < 6 at the time randomization
2. Within 24 hours symptom onset
3. Non-cardioembolic stroke

Intervention : ASA ± ticagrelor
Enrolled patients : 11,016 patients
Outcome : composite of stroke or death at 30d.



N Engl J Med 2020;383:207-17.

THALES trial

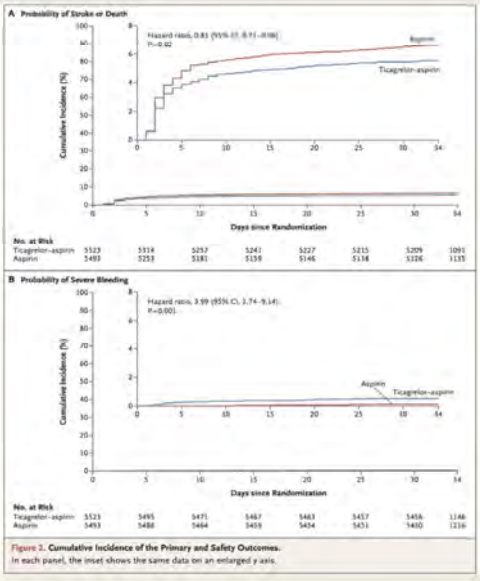


Figure 2. Cumulative Incidence of the Primary and Safety Outcomes.
In each panel, the inset shows the same data on an enlarged y axis.

Composite of stroke or death: 5.5% vs. 6.6%
→ ARD 1.1%

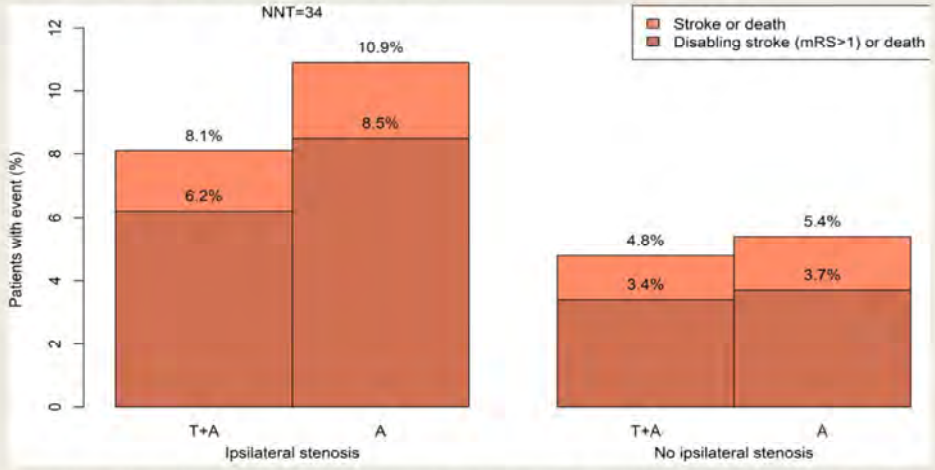
All stroke: 5.1% vs. 6.3%
Ischemic stroke: 5.0% vs. 6.3%

Severe bleeding: 0.5% vs. 0.1%
→ ARD 0.4%

Among patients with a mild-to-moderate acute noncardioembolic ischemic stroke (NIHSS score ≤5) or TIA who were not undergoing intravenous or endovascular thrombolysis, the risk of the composite of stroke or death within 30 days was lower with ticagrelor–aspirin than with aspirin alone.

N Engl J Med 2020;383:207-17.

THALES trial – secondary analysis

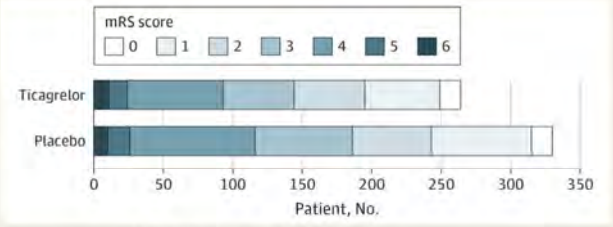


Greater absolute risk reduction of stroke or death at 30 days in patients with ipsilateral atherosclerosis stenosis

Stroke. 2020;51:3504–3513

THALES trial – secondary analysis

Outcome	Ticagrelor (n = 5523) No. of patients (%)	Ticagrelor (n = 5523) Event rate (KM estimate), %	Placebo (n = 5493) No. of patients (%)	Placebo (n = 5493) Event rate (KM estimate), %	HR (95% CI)[a]	*P* value
Primary end point (stroke or death)						
With mRS 0-1 at day 30	70 (1.3)	1.3	87 (1.6)	1.5	0.79 (0.57-1.08)	.14
With mRS >1 at day 30	221 (4.0)	4.0	260 (4.7)	4.7	0.83 (0.69-0.99)	.04
Stroke						
With mRS 0-1 at day 30	70 (1.3)	1.3	87 (1.6)	1.5	0.79 (0.57-1.08)	.14
With mRS >1 at day 30 (including mRS 6)	202 (3.7)	3.7	245 (4.5)	4.5	0.80 (0.67-0.97)	.02
Death	36 (0.7)	0.6	27 (0.5)	0.5	1.28 (0.77-2.11)	.34



Ordinal regression analysis
odds ratio, 0.77; 95%CI, 0.65-0.91; P for ordinal shift = 0.002

Ticagrelor added to aspirin was superior to aspirin alone in preventing disabling stroke or death at 30 days and reduced the total burden of disability

JAMA Neurol. 2021;78(2):177-185.

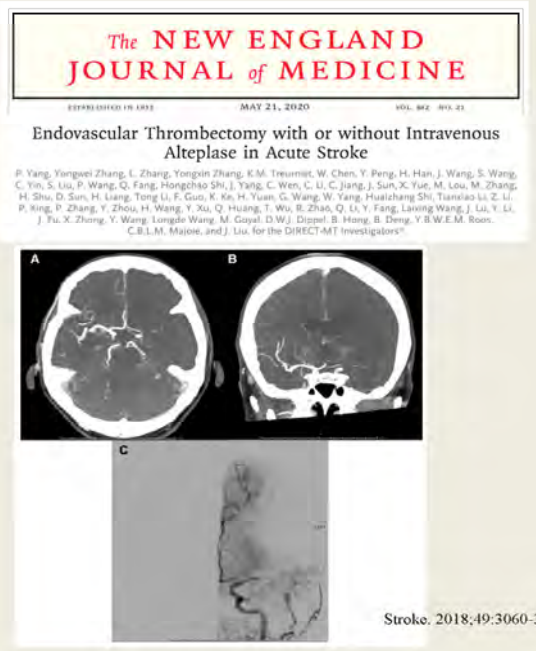
DIRECT-MT trial

IV alteplase before EVT

- ✓ Increase early reperfusion of the ischemic area
- ✓ dissolve residual distal thrombi

⟷

- ✓ lytic effect of intravenous alteplase is limited for large, proximal located thrombi
- ✓ Risk for intracerebral hemorrhage
- ✓ Distal migration of fragmented thrombi



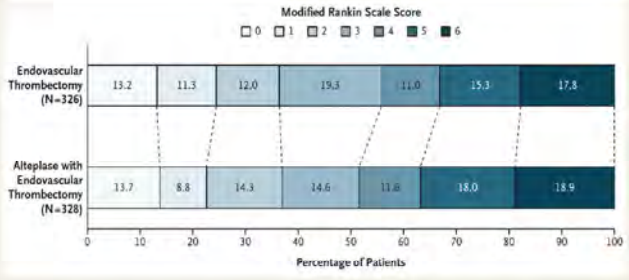
Stroke. 2018;49:3060-3062.

DIRECT-MT trial

Eligibility criteria :
- occlusion in intracranial ICA or M1 or proximal M2
- eligibile for rtPA within 4.5 hours after symptom onset
- NIHSS 2 or more

Intervention : rtPA vs. no rtPA before EVT
Enrolled patients : 656 patients
Outcome : mRS at 90 day.

Non-inferiority margin: adjusted common OR ≥ 0.8



adjusted common OR, 1.07(95% CI, 0.81-1.40)
P for non-inferiority = 0.04

EVT alone was noninferior with regard to functional outcome, to EVT preceded by intravenous rtPA

N Engl J Med 2020;382:1981-93.

SKIP & DEVT trials

- **SKIP trial** (JAMA. 2021;325(3):244-253.)

	Mechanical thrombectomy alone (n = 101)	Intravenous thrombolysis plus mechanical thrombectomy (n = 103)	Noninferiority analysis: Estimate of difference, % (97.5% 1-sided CI)	Noninferiority analysis: Odds ratio (97.5% 1-sided CI)[b]	P value[c]
Primary outcome					
Modified Rankin Scale score 0-2 at 90 d, No. (%)	60 (59.4)	59 (57.3)	2.1 (-11.4 to ∞)	1.09 (0.63 to ∞)	.18

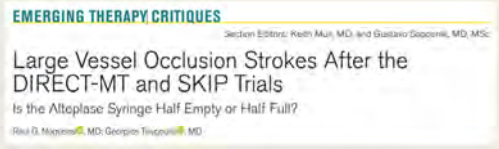
Non-inferiority margin: OR 0.74

- **DEVT trial** (JAMA. 2021;325(3):234-243.)

	No. (%) Endovascular thrombectomy alone (n = 116)	Combined IV thrombolysis and endovascular thrombectomy (n = 118)	Unadjusted difference (95% CI)
Primary efficacy outcome[b]			
Functional independence[c]	63 (54.3)	55 (46.6)	7.7 (−5.1 to ∞)[d]

Non-inferiority margin: -10.0%

DIRECT-MT, SKIP, DEVT trials - critiques

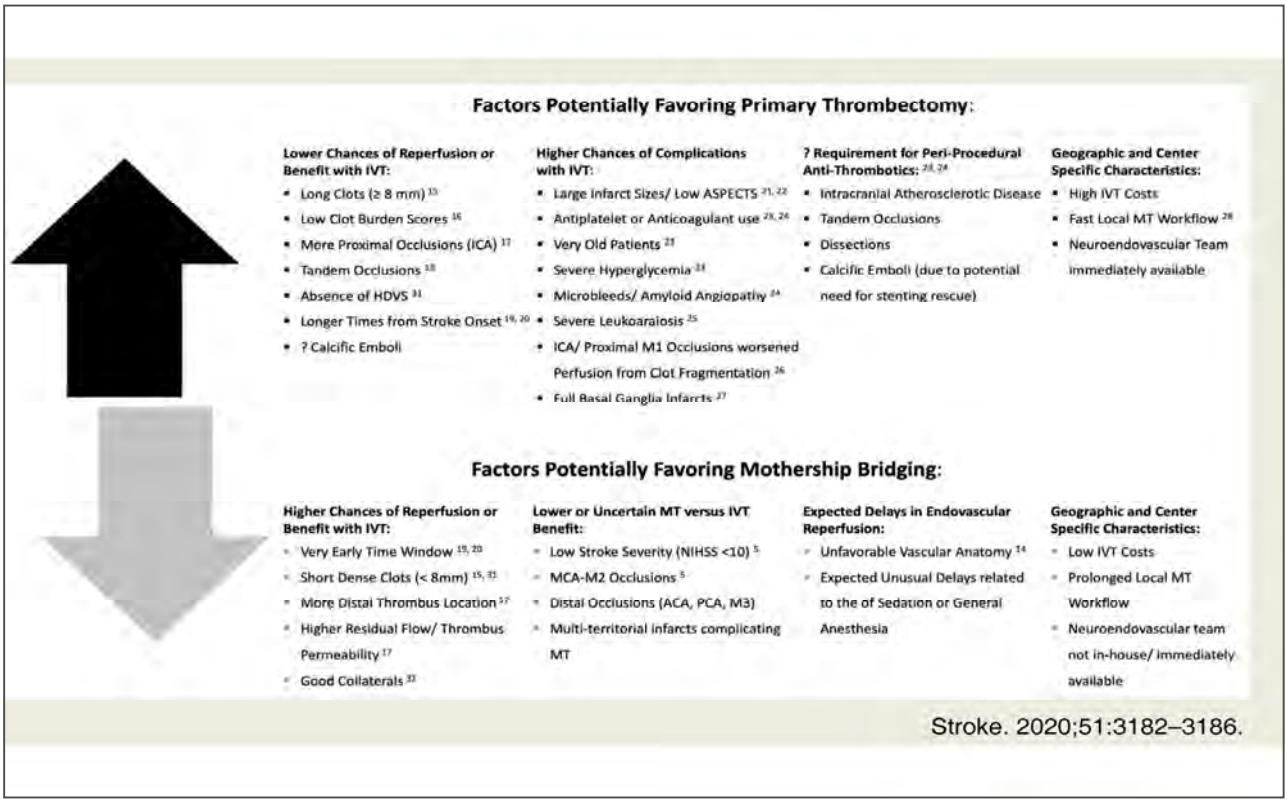

EMERGING THERAPY CRITIQUES

Large Vessel Occlusion Strokes After the DIRECT-MT and SKIP Trials

Is the Alteplase Syringe Half Empty or Half Full?

- Too generous noninferiority margins
  - exceeded the minimal clinically important differences (MCID) expected by stroke expert
- SKIP trial was underpowered
- DIRECT-MT: infusion was completed before MT initiation in only 23 (7%) of the 329 bridging patients
- Neither trial included transferred or drip-and-ship patients
- Generalizability to non-Asian population
  : MR CLEAN-NO IV (ISC 2021), SWIFT-DIRECT, DIRECT-SAFE,

Stroke. 2020;51:3182–3186.



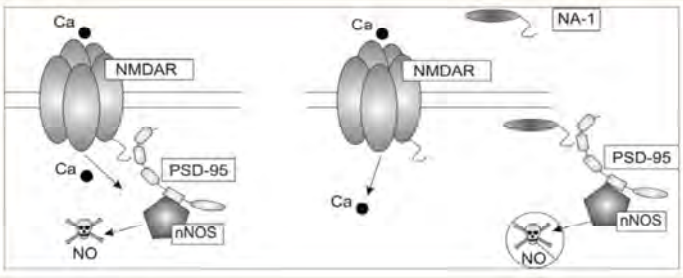
Stroke. 2020;51:3182–3186.

ESCAPE-NA1 trial

- NA-1 is a synthetic, cell-permeant eicosapeptide (20 amino acids) that perturbs protein-protein interactions on the cytosolic surface of the cell membrane mediated by post-synaptic density 95 protein (PSD-95)
- Excellent safety profile in preclinical animal studies, a human Phase 1 trial, and a human Phase 2 study (ENACT trial)
- NA-1 is more effective in reducing infarct size and improving functional outcome in models of ischemia-reperfusion
- ESCAPE patient selection process: eligible patient selection for EVT

Efficacy and safety of nerinetide for the treatment of acute ischaemic stroke (ESCAPE-NA1): a multicentre, double-blind, randomised controlled trial

Michael D Hill, Mayank Goyal, Bijoy K Menon, Ruel G Nogueira, Ryan A McTaggart, Andrew M Demchuk, Alexandre Y Poppe, Brian H Buck, Thalia S Field, Dar Dowlatshahi, Brian A van Adel, Richard H Swartz, Rochir A Shah, Eric Sauvageau, Charlotte Zerna, Johanna M Ospel, Manish Joshi, Mohammed A Almekhlafi, Karla J Ryckborst, Mark W Lowerison, Kathy Hecol, David Garman, Diogo Haussen, Shaunic M Cutting, Shelagh B Coutts, Daniel Roy, Jeremy L Rempel, Axel C R Rohr, Daniela Ianco, Demetrios J Sahlas, Amy Y X Yu, Thomas G Devlin, Ricardo A Hanel, Volker Puetz, Frank L Silver, Bruce C V Campbell, René Chapot, Jeanne Teitelbaum, Jennifer L Mandzia, Timothy J Kleinig, David Turkel-Parrella, Donald Heck, Michael E Kelly, Aditya Bharatha, Oh Young Bang, Ashutosh Jadhav, Rishi Gupta, Donald F Frei, Jason W Tarpley, Cameron G McDougall, Steffan Holmin, Joung-Ho Rha, Ajit S Puri, Marie-Christine Camden, Götz Thomalla, Hana Choe, Stephen J Phillips, Joseph L Schindler, John Thornton, Simon Nogel, Ji Hoe Heo, Sung-Il Sohn, Marios-Nikos Psychogios, Ronald F Buckley, Sidney Starkman, Coleman O Martin, Paul A Burns, Seán Murphy, George A Lopez, Joey English, Michael Tymianski, on behalf of the ESCAPE-NA1 Investigators

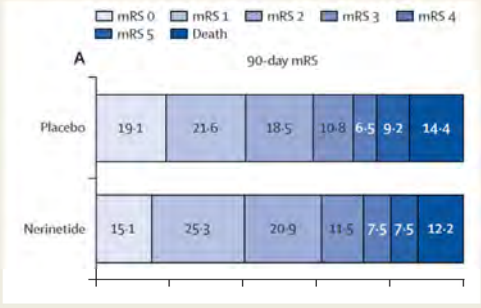


Lancet 2020; 395: 878–87

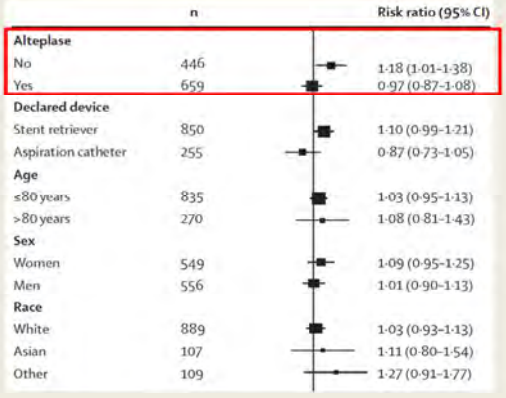
ESCAPE-NA1 trial

- Phase 3, randomized, multicentre, blinded, placebo controlled, parallel group, single-dose design
- Eligibility criteria
  - Within 12 hrs after last-seen well
  - Initial NIHSS > 5
  - Functional independent before stroke
  - Occlusion of intracranial ICA or M1
  - ASPECT 5-10 (small to moderate ischemic core)
  - moderate-to-good collateral circulation (filling more than 50% of MCA pial arterial circulation
- Intervention: single dose IV NA-1 vs. placebo
- Primary efficacy outcome: 90day mRS 0-2

	Adjusted outcomes (prespecified primary analysis), risk ratio (95% CI)	Unadjusted effect size		
		Placebo (n=556)	Nerinetide (n=549)	Risk ratio (95% CI)
Primary outcome				
mRS 0–2	1·04 (0·96 to 1·14)	329 (59·2%)	337 (61·4%)	1·04 (0·94 to 1·14)
Secondary outcomes				
NIHSS 0–2	1·01 (0·92 to 1·11)	320 (57·6%)	320 (58·3%)	1·01 (0·92 to 1·12)
mBI 95–100	1·03 (0·94 to 1·12)	335 (60·3%)	341 (62·1%)	1·03 (0·94 to 1·13)
Mortality*	0·84 (0·63 to 1·13)	80 (14·4%)	67 (12·2%)	0·85 (0·63 to 1·15)
mRS 0–1	0·98 (0·85 to 1·12)	226 (40·6%)	222 (40·4%)	0·99 (0·86 to 1·15)
Infarct volume	−0·29 (−0·87 to 0·30)†	26·0 (6·6 to 101·5)‡	23·7 (6·4 to 78·9)‡	−2·35



ESCAPE-NA1 trial



- Effect modification by rtPA
  - drug–drug interaction between alteplase and nerinetide
  - nerinetide has amino acid sequences known to be cleaved by plasmin, a serine protease generated from circulating plasminogen by tissue-plasminogen activators
- **ESCAPE-NEXT trial**

Summary

- ✓ TST trial: LDL target <70mg/dL is beneficial in patients with atherosclerotic stroke
- ✓ THALES trial: Early use of aspirin+ticagrelor combination is another option for patients with minor stroke or high-risk TIA
- ✓ DIRECT-MT, SKIP, DEVT trials: utility and efficacy of rtPA before EVT is still not answered, the decision may be personalized in the future
- ✓ ESCAPE-NA1 trial: possible benefit of nerinetide in patients who undergo EVT
  → hope to be answered by the ESCAPE-NEXT trial