

Stroke



이 건 주

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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

Although 2020 has been marked by the evolution of the COVID-19 pandemic, important advances in much of research have been reported, particularly in stroke treatment and secondary prevention.

In 2008, the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial showed the benefit of intensive statin treatment (atorvastatin 80 mg daily) in secondary stroke prevention. Almost 12 years later, the effect of intensive reduction of LDL cholesterol after a recent ischemic stroke or transient ischemic attack in the setting of atherothrombotic disease was assessed in the Treat Stroke to Target trial¹, a parallel group, single-blind, randomized trial done at 77 sites in France and South Korea. Almost 3000 patients were randomly assigned either an LDL target of less than 70 mg/dL (lower target group) or a target range of 90–120 mg/dL (higher target group). During follow-up of median 3.5 years (IQR 2.0–6.7), patients allocated to the lower target group had reduced risk for the composite primary endpoint of major cardiovascular events compared with patients in the higher target group. More than 65% of composite major cardiovascular events in both groups were ischemic, instead of venous or undetermined origin, highlighting the increased stroke risk in this population. The absolute risk of intracranial hemorrhage was small, and similar in the lower and the higher target group. These trial results corroborate those of SPARCL and emphasize intensive lipid management as a valid therapeutic target in secondary atherothrombotic stroke prevention.

In a series of two independent randomized trials, dual antiplatelet treatment with aspirin and clopidogrel was shown to be superior to aspirin monotherapy in patients after a minor acute ischemic stroke or a transient ischemic attack. A subsequent double-blind randomized trial—The Acute Stroke or Transient Ischemic Attack Treated with Ticagrelor and ASA for Prevention of Stroke and Death (THALES)—done at 434 sites in 28 countries compared the antiplatelet ticagrelor (180 mg loading dose followed by 90 mg twice daily) in addition to aspirin (100–225 mg on the first day followed by 75–100 mg daily) with aspirin alone within 24 h of onset of a minor non-cardioembolic acute ischemic stroke or transient ischemic attack. The combination of ticagrelor with aspirin was associated with lower rates of stroke or fatal events, a lower rate of ischemic stroke events, and more severe bleeding episodes within 30 days of follow-up, compared with aspirin monotherapy. Although THALES reiterates the benefit of short-term dual antiplatelet treatment, any additional value from using ticagrelor instead of clopidogrel remains uncertain.

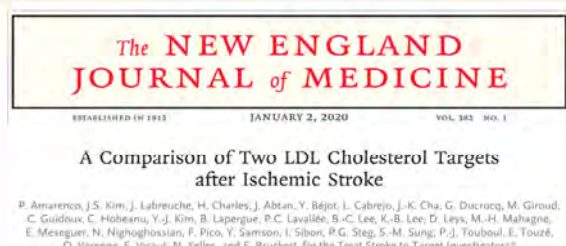
Although several observational cohort studies have investigated intravenous thrombolysis before endovascular thrombectomy (the Endovascular Thrombectomy with or without Intravenous Alteplase in Acute Stroke trial)² to the first to address the hypothesis that endovascular thrombectomy alone is not inferior to the combination of endovascular thrombectomy preceded by intravenous alteplase in patients eligible for both treatments. After enrolling 853 patients at 43 academic centers in China, endovascular thrombectomy alone within 4.5 h of stroke onset was shown to be non-inferior to endovascular thrombectomy preceded by intravenous alteplase with respect to 3-month functional outcomes. Safety and efficacy outcomes did not differ between the two groups, except that successful reperfusion before endovascular thrombectomy occurred more frequently in the combined intravenous alteplase and endovascular thrombectomy group (2.4% vs 7.0%). Taking into account the 20% wide non-inferiority margin with respect to functional outcome, the difference between groups in the percentages of enrolled patients not receiving endovascular thrombectomy, and the many patients allocated combination treatment who did not receive the full dose of alteplase, in addition to the fact that alteplase is not contraindicated in China, this research question still remains open and will hopefully be answered soon by other ongoing randomized trials³.

Although endovascular thrombectomy has substantially improved functional outcomes of patients with acute ischemic stroke, many treated individuals die or are left severely disabled. The Efficacy and Safety of Nerinetide for Treatment of Acute Ischemic Stroke trial was the first randomized trial to assess the safety and efficacy of a neuroprotectant within the endovascular thrombectomy setting⁴. Around 3000 adult patients eligible for endovascular thrombectomy up to 12 h after symptom onset were randomly allocated either intravenous nerinetide (one dose of 2.6 mg/kg) or placebo. Nerinetide did not increase the likelihood of good

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



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).

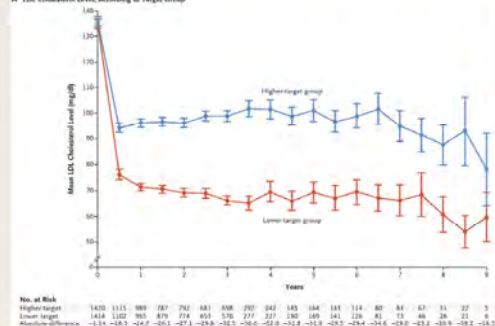
2014 AHA/ASA Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack

Treat Stroke to Target (TST) trial

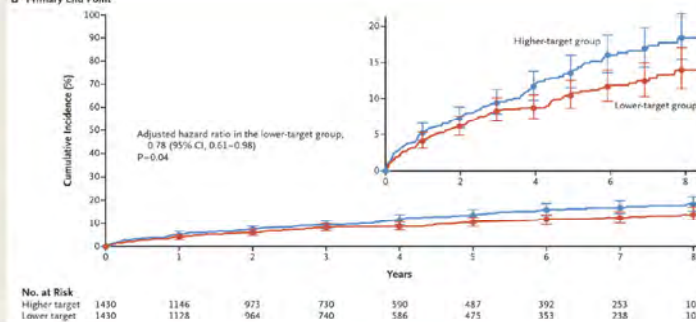
- ✓ Korean & French patients
 - Korean patients were enrolled later in the trial
- ✓ **Eligibility criteria**
 - Ischemic stroke within 3 months (TIA within 2 weeks)
 - mRS 0-3
 - Atherosclerotic stroke: ipsilateral or contralateral stenosis of intra/extracerebral artery at least 4mm plaque of the aortic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

A LDL Cholesterol Level, According to Target Group



B Primary End Point



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

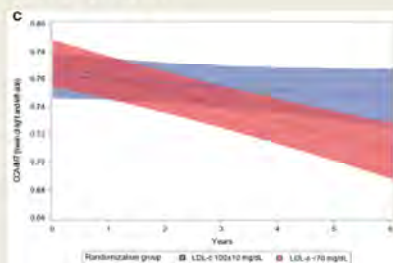
Primary efficacy outcome: 8.5% vs. 10.9%

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 100-120 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, $\mu\text{m/y}$ (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., Liying 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., Hailin Xia, M.D., and S. Claiborne Johnston, M.D., Ph.D., for the CHANCE Investigators^a

POINT, 2018

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

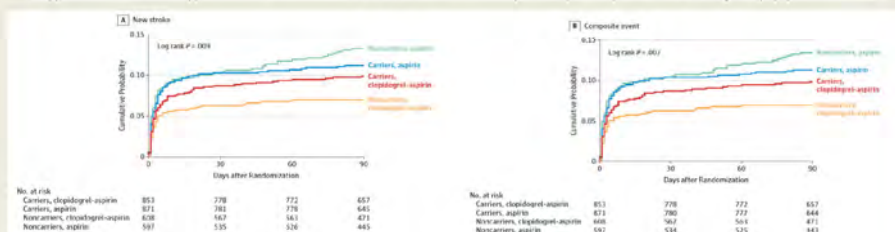
S. Claiborne Johnston, M.D., Ph.D., J. Donald Easton, M.D., Mary Farrant, M.B.A., William Barsan, M.D., Robin A. Conwit, M.D., Jordan J. Elm, Ph.D., Anthony S. Kim, M.D., Anne S. Lindblad, Ph.D., and Yuen Y. Palevsky, Ph.D., for the Clinical Research Collaboration: Neurological Emergencies Treatment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

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

Outcome	Carriers ^a					Noncarriers ^b				
	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
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
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
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
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
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



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

THALES trial

Acute STroke or Transient Ischemic Attack Treated With Ticagrelor and ASA for Prevention of Stroke and Death (THALES)

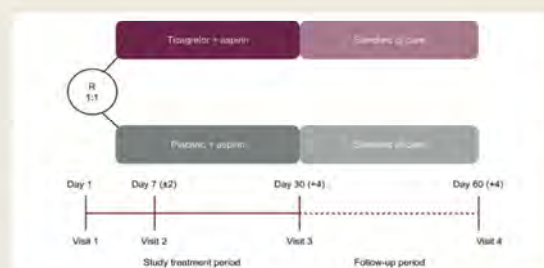
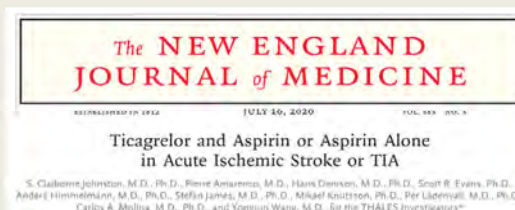
Subject : TIA or minor acute ischemic stroke

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

Intervention : ASA ± ticagrelor

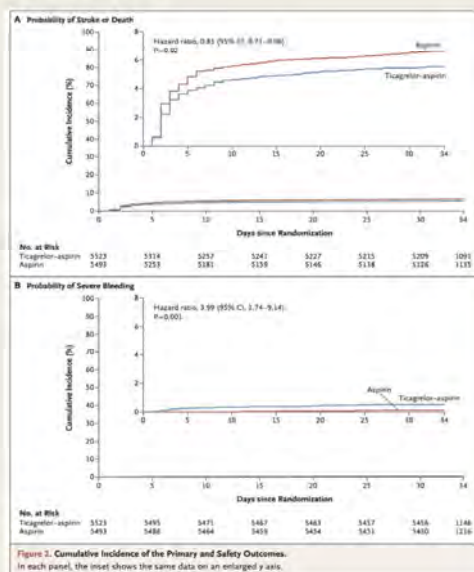
Enrolled patients : 11,016 patients

Outcome : composite of stroke or death at 30d.



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

THALES trial



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

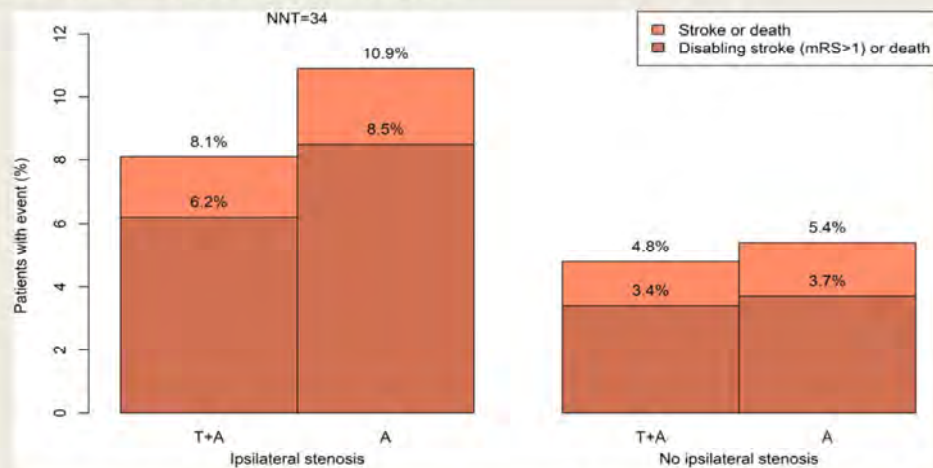
All stroke: 5.1% vs. 6.3%
Ischemic stroke: 5.0% vs. 6.3%

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

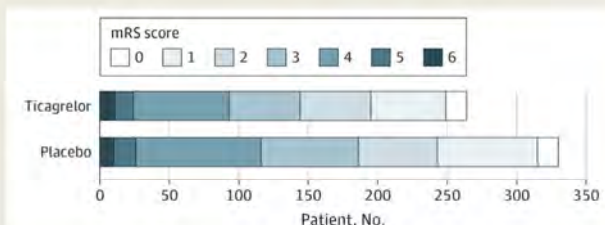


Greater absolute risk reduction of stroke or death at 30 days in patients with ipsilateral atherosclerosis stenosis

Stroke. 2020;51:3504–3513

THALES trial – secondary analysis

Outcome	Ticagrelor (n = 5523)		Placebo (n = 5493)		HR (95% CI) ^a	P value
	No. of patients (%)	Event rate (KM estimate), %	No. of patients (%)	Event rate (KM estimate), %		
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.

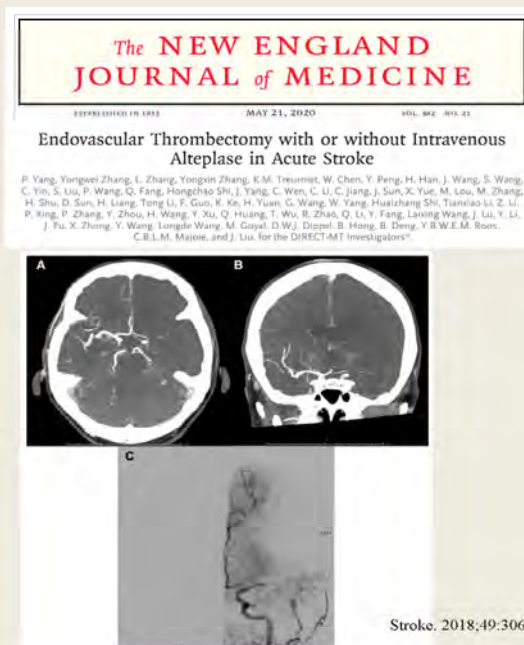
DIRECT-MT trial

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



DIRECT-MT trial

Eligibility criteria :

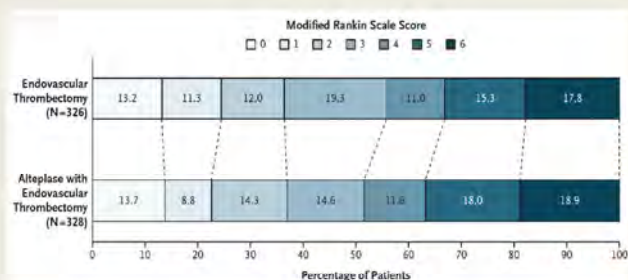
- occlusion in intracranial ICA or M1 or proximal M2
- eligible for rtPA within 4.5 hours after symptom onset
- NIHSS 2 or more

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)	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 ^a			
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

Section Editors: Reethi Mui, MD, and Gustavo Gasparrini, MD, MSc

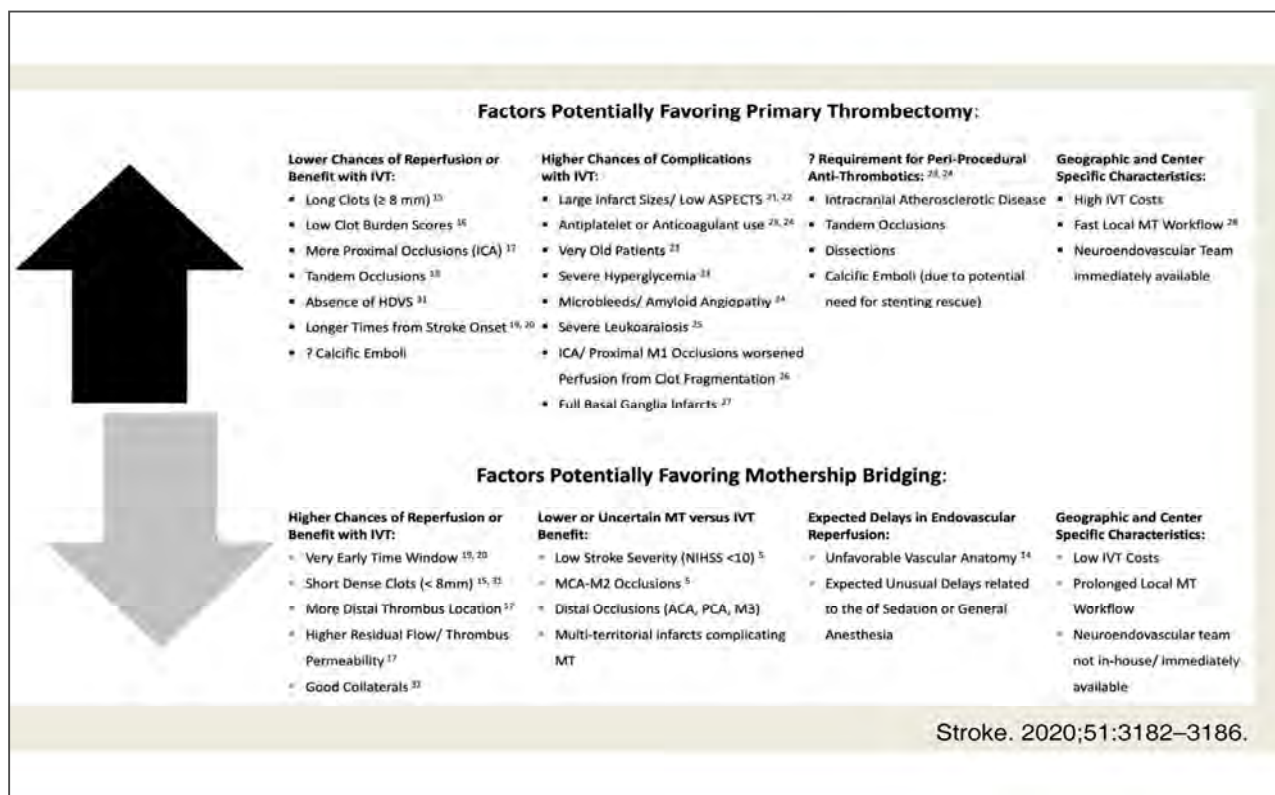
Large Vessel Occlusion Strokes After the DIRECT-MT and SKIP Trials

Is the Alteplase Syringe Half Empty or Half Full?

Rishi D. Nijmeh, MD, Georgetown University, MD

- 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.



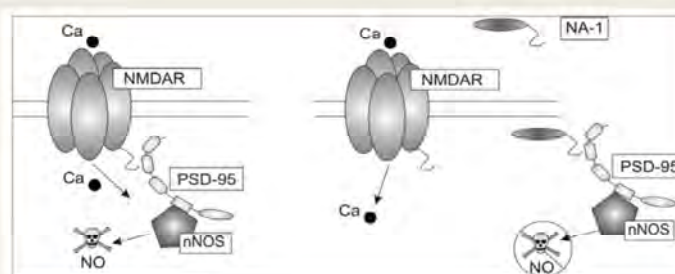
ESCAPE-NA1 trial

- 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

Muhammad D HJ, Mayank Gopal, Rishi K Menon, Paul G Nagesh, Ryan A McTaggart, Andrew M Demchuk, Alexandre Y Poppo, Brian H Bock, Thalia S Fink, Daz Dowlatabadi, Brian A van der, Richard H Swartz, Ruchir A Shah, Eric Sauvageau, Charlotte Zerna, Johanna M O'Neil, Mariah Joshi, Mohammed A Almekhlafi, Karlo J Ryckborst, Mark W Loverson, Kathy Heon, David German, Diego Hausman, Shauna M Cutting, Shalagh B Coates, Daniel Roy, Jeremy L Rempel, Axel C R Kohn, Donatella Jancu, Demetris J Sahlas, Amy Y X Yu, Thomas G Dewlin, Ricardo A Hanel, Valter Puetz, Frank L Shum, Bruce CV Campbell, René Chaput, Joanne Trifunovic, Jennifer L Mandala, Timothy J Rainey, David Turkel-Pearl, Donald Heck, Michael E Kelly, Aditya Bharathi, Oh Young Bang, Ashutosh Jadhav, Rishi Gupta, Donald F Frei, Jason W Tongley, Cameron G McGough, Steffen Holmin, Joon-Ho Rhee, Apt S Puri, Marie Christine Carmona, Gatz Thoma, Hana Choi, Stephen J Phillips, Joseph L Schellinger, John Thornton, Simon Nagel, Ji-Hae Hoo, Sung-Ho Suh, Marlos Nikos Psychogiannis, Ronald F Budzik, Sidney Starkman, Coleman O Martin, Paul A Ikem, Selen Murphy, George A Lopez, Joey English, Michael Tymianski, on behalf of the ESCAPE-NA1 Investigators

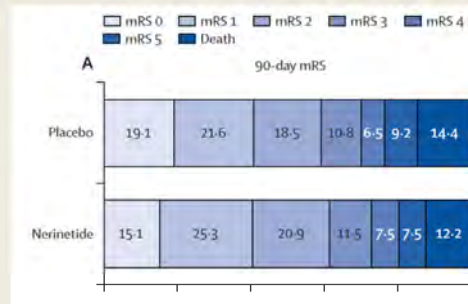


Lancet 2020; 395: 878–87

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

	n	Risk ratio (95% CI)
Alteplase		
No	446	1.18 (1.01-1.38)
Yes	659	0.97 (0.87-1.08)
Declared device		
Stent retriever	850	1.10 (0.99-1.21)
Aspiration catheter	255	0.87 (0.73-1.05)
Age		
≤80 years	835	1.03 (0.95-1.13)
>80 years	270	1.08 (0.81-1.43)
Sex		
Women	549	1.09 (0.95-1.25)
Men	556	1.01 (0.90-1.13)
Race		
White	889	1.03 (0.93-1.13)
Asian	107	1.11 (0.80-1.54)
Other	109	1.27 (0.91-1.77)

- 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

NIH U.S. National Library of Medicine
ClinicalTrials.gov

ClinicalTrials.gov Identifier: NCT04462536

Recruitment Status: Recruiting
First Posted: July 8, 2020
Last Update Posted: December 17, 2020
See [Contacts and Locations](#)

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