Trial/Paper	Population/ Aim	Treatment Assignment	Design	Setting	Period	N. Patients	Main Results	Conclusion
Prevention								
THALES (NEJM)[1]	Population: Patients with mild to moderate acute non-cardioembolic ischemic stroke, with a NIHSS ≤ 5, or TIA, who were not undergoing thrombolysis or thrombectomy. Aim: To investigate whether ticagrelor and aspirin is more effective than aspirin alone (with placebo) in the prevention of new stroke events.	**Ticagrelor arm:** Day 1, loading dose of ticagrelor 180 mg, followed by daily maintenance dose 90 mg twice daily until day 30. **Placebo arm:** Day 1, loading dose of placebo followed by placebo daily maintenance dose until day 30.	Randomized, placebo-controlled, double-blind trial	Global (388 Sites)	January 22, 2018, and October 7, 2019	11,016	• 5523 in TA group, 5493 in Asp only. • Primary outcome (stroke and death in 30 days): 5.5% in TA vs 6.6% in Asp only (HR: 0.83; 95% CI – 0.71-0.96, p=0.02). • New stroke in 5% in TA, 6.3% in A only (HR: 0.79; 95% CI – 0.68-0.93, p=0.004). • No difference in disability (TA: 23.8% vs A only: 24.1%). • More frequent severe bleeding (TA:0.5% vs A only 0.1%, p=0.001), • ICH or fatal bleeding (0.4% vs 0.1%, p=0.005) • Discontinuation of medication due to bleeding (2.8% vs 0.6%, p<0.001)	Among patients with a mild ischemic stroke (NIHSS≤5) or TIA, the risk of the **composite of stroke or death** within 30 days was **<u>lower</u>** with ticagrelor plus aspirin vs aspirin alone, but there was no significant difference in the incidence of disability. **Severe bleeding** occurred **<u>more frequently</u>** with ticagrelor.
RIVER Trial (NEJM)[2]	Population: Adults who had atrial fibrillation or flutter and a bioprosthetic mitral valve and were receiving oral anticoagulation for thromboembolism prophylaxis Aim: To assess the efficacy and safety of rivaroxaban as compared with warfarin among patients with atrial fibrillation and a bioprosthetic mitral valve	**Rivaroxaban arm:** (20 mg once daily) **Warfarin** dose-adjusted (target international normalized ratio, 2.0 to 3.0)	Multicenter randomized, noninferiority, open-label design with blinded adjudication of outcomes **Primary outcome** was a composite of death, major cardiovascular events (stroke, TIA, systemic embolism, valve thrombosis, or hospitalization for heart failure), or major bleeding at 12 months	49 sites in Brazil	April 14, 2016, through July 22, 2019	1005	• Rivaroxaban (500) vs warfarin (505) • A primary-outcome event occurred at a mean of 347.5 days in the rivaroxaban group and 340.1 days in the warfarin group (difference calculated as restricted mean survival time, 7.4 days; 95% confidence interval [CI], −1.4 to 16.3; P<0.001) • Death: 3.4% in NOAC vs 5.1% in warfarin, HR 0.65 (95%CI: 0.35-1.2) • Any stroke: 0.6% vs 2.4; HR 0.25 (0.07-0.88) • Ischemic stroke: 0.6% vs 1.4% HR 0.43 (0.11-1.66)	Rivaroxaban was found to be noninferior to warfarin among patients with atrial fibrillation and a bioprosthetic mitral valve in regard to mean time until the primary outcome of death, major cardiovascular events, or major bleeding at 12 months.

Trial/Paper	Population/Aim	Arms	Design	Setting	Period	N. Patients	Main Results	Conclusion
Treat Stroke to Target Trial (NEJM)[3]	Population: Adults (>18 y) with ischemic stroke within 3 months and stable neurological deficit; or TIA within 15 days with atherosclerotic disease of cerebral artery, coronary artery or aorta, and an indication to receive statins. Aim: To evaluate if a target level of LDL cholesterol of less than 70 mg/dL would be superior to a target range of 90 mg to 110 mg/dL in reducing overall cardiovascular events after an ischemic stroke or a TIA among patients with evidence of atherosclerosis.	**Target LDL level of <70 mg/dL** **vs** **Target LDL level of 90-100 mg/dL** Any statin could be used to achieve target LDL level	International, multicenter, randomized, parallel arm, open-label design with blinded adjudication of the endpoint **Primary outcome** was non-fatal stroke, non-fatal MI, unstable angina with urgent intervention, TIA with urgent carotid artery intervention or cardiovascular (including unexplained) death	77 sites in France and South Korea	March 2010 to December, 2018	2860	• Primary endpoint: Less frequent in lower LDL target group (8.5% vs 10.9%, HR: 0.78, 95% CI: 0.61-0.98, p=0.04) • Pre-specified adjusted analysis also demonstrated similar effect (adj. HR: 0.78, 95% CI: 0.62-0.98) • Two-thirds of the events meeting primary endpoint definition were non-fatal strokes. • No secondary endpoints reached statistical significance.	Among patients with an ischemic stroke or TIA and with evidence of atherosclerotic disease, those with a target LDL cholesterol level of <70 mg/dL exhibited lower risk of composite endpoint of major cardiovascular event compared with patients with a target LDL level of 90-100 mg/dL.

Trial/Paper	Population/Aim	Arms	Design	Setting	Period	N. Patients	Main Results	Conclusion
Thrombectomy								
Bridging Therapy with Thrombolytics								
DIRECT-MT (NEJM)[4]	Population: Adults who had an LVO in ICA or M1, or both that could be treated with tPA in 4.5 hours; and had NIHSS ≥ 2 Aim: To assess whether direct EVT is non-inferior compared with combined IVT plus EVT	**Intervention:** Endovascular thrombectomy alone **Control:** EVT preceded by tPA, at a dose of 0.9 mg/kg of weight, within 4.5 hours	Investigator-initiated, multicenter, randomized, open-label trial with blinded outcome assessment	41 academic tertiary care centers in China	February 23, 2018, through July 2, 2019	656	• 327 EVT only, 329 EVT+tPA • EVT only non-inferior to EVT + tPA (acOR: 1.07, 95% CI- 0.81-1.40, p=0.04 for non-inferiority) • Lower rates of initial recanalization before procedure (EVT only 2.4% vs EVT + tPA – 7.0%) • Lower rates of eTICI 2b-3 (EVT only 79.4% vs 84.5%; OR 0.70 (0.47 to 1.06) • Similar mortality rates: 17.7% vs 18.8%, p=0.71; • sICH: 4.3% vs 6.1%, p=0.64	Among Chinese patients with LVO, thrombectomy alone was noninferior with regard to functional outcomes, within a 20% margin of confidence, to EVT preceded by tPA within 4.5 hours of LKW.

- Significant crossover: 31+17 total without EVT
- Only patients presenting to EVT capable centers
- 86.5% completed tPA transfusion during EVT (didn't complete before the beginning of EVT)
- Large non-inferiority margin: 20%, compared with other trials with 2% to 4% margins

Trial/Paper	Population/ Aim	Arms	Design	Setting	Period	N. Patients	Main Results	Conclusion
SKIP (JAMA)[6,]**	Population: Patients aged 18 to 85 years with ICA or M1 occlusion, and able to puncture within 4 hours. With DWI-ASPECTS more than 5 or CT-ASPECTS more than 6 with NIHSS >6 Aim: To examine whether mechanical thrombectomy alone is noninferior to combined intravenous thrombolysis plus mechanical thrombectomy for favorable poststroke outcome	**Intervention**: Direct EVT group was administered EVT without IVT **Control**: Bridging therapy group was administered IVT preceding EVT. rtPA was administered at 0.6 mg/kg body weight up to a maximum of 60 mg	Multicenter, randomized, open-label, noninferiority clinical trial	23 hospital networks in Japan	January 2017, to July 2019, with final follow-up in October 2019	204	• 101 dEVT vs 103 bridge • Primary outcome: (mRS) of 0 to 2 at 90 days: 59.4% in dEVT vs 57.3% in Bridge; OR: 1.09 [1-sided 97.5% CI, 0.63 to ∞]; P = 0.18 for noninferiority • Shift: cOR: 0.97 [1-sided 97.5% CI, 0.60 to ∞]; noninferiority P = 0.27 • Mortality: 7.9% in dEVT vs 8.7% in Bridge, OR: 0.90 [95% CI, 0.33 to 2.43]; P > 0.99 • eTICI >=2b: 0.66 [95% CI, 0.24 to 1.82]; P = 0.46 • Lower Any ICH with dEVT: 33.7% vs 50.5% BT, OR: 0.50; 95% CI, 0.28 to 0.88; P=0.02 • sICH (NINDS) OR: 0.65; 95% CI, 0.25 to 1.67; P=0.48 • sICH (SITS MOST) OR: 0.75; 95% CI, 0.25 to 2.24; P=0.78	EVT alone failed to demonstrate noninferiority regarding favorable functional outcomes compared with combined IV thrombolysis plus EVT among patients with acute LVO stroke. It is important to note, however, that the wide confidence intervals around the effect estimate did not permit a conclusion of inferiority.

- Large non-inferiority margin (25%)
- Limited enrollment (~100 in each group)
- Use of low-dose tPA (0.6mg/kg)

** The podcast discussed the results presented in ISC 2020 using information obtained from https://professional.heart.org/en/science-news/skip-study-clinical-trial-details. The trial manuscript was published recently on January 19, 2021 and the results provided above reflects the published results.

Trial/Paper	Population/Aim	Arms	Design	Setting	Period	N. Patients	Main Results	Conclusion
Triage								
RACECAT (not published)[6]	Population: Patients with suspected LVO identified by EMS by RACE>4 in areas in which the stroke center is not EVT-capable Aim: To assess 90-day outcomes in LVO (by EMS) in direct transfer to an endovascular stroke senter, compared with transfer to the closest local stroke center.	**Intervention**: Transfer to the nearest endovascular center **Control**: Transfer to a local stroke center based on current stroke code protocols	Prospective, multicenter, cluster randomized, controlled, open, blinded-endpoint trial RACE scale score >4/9	Catalonia, Spain (27 hospitals)		1401	• Primary outcome: 90-day mRS in AIS (adj HR 1.029) • Higher rate of thrombectomy in bypass: 50% vs 40% • Shorter LKW to GP in bypass: 214 vs 270 minutes • 25% of patients had hemorrhagic stroke • Complications during transfers 1% (bypass) vs 0.5% (local)	Direct transfer to an EVT center that is a greater distance away than a local primary stroke center is not necessarily associated with improved functional outcomes among patients with suspected LVO.
Low Economic Setting								
RESILIENT (NEJM)[7]	Population: Patients with anterior circulation LVO that could be treated within 8 hours Aim: To determine the safety and efficacy of thrombectomy with medical therapy compared with medical therapy alone in Brazil (a developing country).	**Intervention**: Thrombectomy + MM **Control**: Guideline-based care alone, including tPA, for eligible patients within 4.5 hours	Multicenter, prospective, randomized, open-label, controlled trial with blinded central evaluation of outcomes Patients with LVO in the anterior circulation within 8 hours of LKW	12 sites	January 2017 through March 2019	221	• 111 EVT vs 110 MM only • Primary outcome: Shift on 90-day mRS – acOR: 2.28 (95% CI, 1.41 to 3.69; P=0.001) • mRS 0-2: 35.1% vs 20%, aOR: 2.55 (95% CI 1.34-4.88) • mTICI >=2b: 82% in EVT group • Mortality: 24.3% vs 30%, OR 0.75, 95% 0.41-1.36 • sICH (SITS MOST): 4.5% vs 4.5%, OR: 0.99 (0.26-3.78)	Endovascular treatment within 8 hours post-stroke onset combined with standard care was associated with better functional outcomes at 90 days.

Trial/Paper	Population/ Aim	Arms	Design	Setting	Period	N. Patients	Main Results	Conclusion
Posterior Circulation								
BASILAR (JAMA Neuro)[8]	Population: Patients with acute BAO within 24 hours, who could be treated with intravenous rt-PA within 4.5 hours or intravenous urokinase within 6 hours Aim: To examine the relationship between EVT and clinical outcomes in acute BAO	**Intervention**: EVT+MM group **Control**: MM *According to the treatment they received*	**Nonrandomized** cohort study (prospective registry of consecutive patients)	47 comprehensive stroke centers in China	January 2014 and May 2019	829	• 647 EVT vs 182 MM only • Primary outcome: Shift on 90-day mRS – acOR: 3.08 (95% CI, 2.09-4.55; P < .001) • mRS 0-2: 27.4% vs 7.1%, aOR: 4.9 (95% CI 2.41-9.87; P <0.001) • mTICI≥2b: 80.7% in EVT group • Mortality: 46.2% vs 71.4%, aOR: 2.91 (95% CI 1.95-4.40; P <0.001) • sICH (Heidelberg): 7.1% vs 0.5%; p <0.001 • NIHSS change from baseline at 5 to 7 days: -2 (-12 to 3) vs +1 (- to 9.5), acOR: -6.28 (95% CI, (-8.33) – (-4.21); P < .001)	EVT that was administered within 24 hours of estimated occlusion time was found to be associated with better functional outcomes and decreased mortality among patients with acute BAO.

Trial/Paper	Population/ Aim	Arms	Design	Setting	Period	N. Patients	Main Results	Conclusion
BEST (Lancet Neurology)[9]	Population: Patients with occlusion of the basilar artery or distal intracranial vertebral artery (V4 segment), could be randomly assigned within 8 hours of estimated occlusion time Aim: To evaluate the efficacy and safety of endovascular treatment of acute strokes due to vertebrobasilar artery occlusion	**Intervention**: EVT+MM group **Control**: MM	Multicenter, randomized, open-label trial, with blinded outcome assessment presenting within 8 hours of vertebrobasilar occlusion	28 centers in China	April 27, 2015, and September 27, 2017	131	• 66 EVT vs 65 MM only • Primary outcome: mRS 0-3: 42% vs 32%; acOR: 1·74, (95% CI 0·81–3·74; P=0.23) • mRS 0-2: 33% vs 28%, aOR: 1.4 (95% CI 0.64-3.10; P =0.48) • Shift on 90-day mRS – acOR: 1.36 (95% CI, 0.72-2.55; P =0.69) • mTICI≥2b: 71% in EVT group • Mortality: 33% vs 38%, OR: 0.8 (95% CI 0.37-1.64; P =0.54) • sICH (hemorrhage with ≥4 NIHSS in 24 hrs.): 8% vs 0%; p =0.06	The study did not find that there was any evidence of difference in favorable outcomes among patients who received endovascular therapy vs those who received standard medical therapy alone. The results may have been confounded by poor adherence to the assigned study treatment and a reduced sample size due to early termination.

- Crossover from control to intervention: 14 (22%)
- Crossover from intervention to control: 3 (5%)

Trial/Paper	Population/ Aim	Arms	Design	Setting	Period	N. Patients	Main Results	Conclusion
Image Selection								
SELECT[10]	Population: Adults with NIHSS ≥ 6 due to LVO in anterior circulation ICA or M1/M2 Aim: To optimize the imaging selection for endovascular thrombectomy among patients with acute ischemic stroke presenting with LVO in up to 24 hours from last known well	**Intervention:** Endovascular thrombectomy + best medical management including IV tPA **Control:** Best medical management, including IV tPA	Prospective, Multicenter Cohort	9 high-volume EVT centers across the US	January 2016 to February 2018	361	• 285 EVTs, 76 MMs • Of 285 EVTs, favorable profiles on CT in 87%; favorable profiles on CTP in 91%. • 81% patients had favorable profiles on both CT and CTP, 3% both unfavorable, 16% discordant • Similar functional independence with favorable profiles favorable CT: 56% vs favorable CTP: 57%, adj. OR 1.91, 95% CI: 0.40–9.01, p = 0.41 • Functional independence: Both favorable: 58%, discordant: 38%, both unfavorable: 0% • Favorable CT/unfavorable CTP: FI: 24%, sICH: 24%, Mortality: 53%; Unfavorable CT/favorable CTP: FI: 46%, sICH: 4%, Mortality: 11%	• Most of the EVT patients demonstrated a concordant favorable profile on both CT and CTP. • A favorable profile on CT was associated with similar functional independence as a favorable profile on CTP. • Patients with a favorable profile on both imaging modalities had the highest functional independence, followed by patients with discordant imaging profiles. • Patients with favorable CT but unfavorable CT profile had higher rates of sICH and mortality following EVT, but EVT still was better than medical management.

Trial/Paper	Population/ Aim	Arms	Design	Setting	Period	N. Patients	Main Results	Conclusion
Large Core								
SELECT Large Core[11]	Population: Adults with NIHSS ≥ 6 due to LVO in anterior circulation ICA or M1/M2 with ASPECTS ≤ 5 or an ischemic core volume of 50 cm Aim: A subgroup analysis of SELECT among patients with ASPECTS <5 or ischemic core ≥ 50 cc, or both	**Intervention:** Endovascular thrombectomy + best medical management including IV tPA **Control:** Best medical management, including IV tPA	Prospective, multicenter cohort	9 high-volume EVT centers across the US	January 2016 to February 2018	105	• 62 EVTs, 43 MMs • Functional independence: EVT: 31% vs MM 14%, OR: 3.27, 95% CI: 1.11-9.62, p=0.03 • sICH: EVT 13% vs MM: 7%, p=0.51 • Mortality: 29% vs 42%, p=0.17 • 42% reduction in functional independence with every 10 ml increase in infarct core (aOR: 58, 95% CI: 0.39-0.87), p=0.007).	The findings of this exploratory analysis indicated that EVT was associated with better functional independence and similar safety profile among patients with large core strokes. The odds of functional independence decreased by 42% with each 10-cc increase.

Trial/Paper	Aim	Arms	Design	Setting	Period	N. Patients	Main Results	Conclusion
Thrombolysis								
Extending Window Beyond 4.5 Hours								
Tsivgoulis et al. (Neurology)[12]	Population: Adults with AIS receiving treatment with IV alteplase (0.9 mg/kg) either in the setting of unknown symptom onset time (wake-up strokes) or >4.5 hours from onset selected by advanced baseline neuroimaging with either CT or MRI Aim: To examine the efficacy of IV thrombolysis treatment among patients with acute ischemic stroke who had a symptom onset time that was unclear or fell outside the 4.5-hour window designated by advanced neuroimaging	**Intervention**: tPA (0.9 mg/kg) **Control**: no thrombolysis	Random-effects meta-analyses (WAKE-UP, EXTEND, THAWS, and ECASS-4)	WAKE-UP was a European randomized, placebo-controlled trial used MRI with DWI-FLAIR mismatch EXTEND was a trial in Australia, Finland, New Zealand, and Taiwan using penumbral imaging with either CT or MRI perfusion. THAWS was a Japanese trial using MRI with DWI-FLAIR mismatch. ECASS-4 was a European trial, in Austria, Czech Republic, France, Germany, Italy, Spain, UK, perfusion-diff MRI/		859	• mRS 0-1 (odds ratio [OR] 1.48, 95% confidence interval [CI] 1.12–1.96), aOR: 1.62, 95% CI 1.20–2.20 • mRS 0-2 (OR 1.42, 95% CI 1.07–1.90), aOR: 1.42, 95% CI 1.11–1.81 • sICH (OR 5.28, 95% CI 1.35–20.68), aOR: 6.22, 95% CI 1.37–28.26 • Complete recanalization (OR 3.29, 95% CI 1.90–5.69) • Mortality: 1.75, 95% CI 0.93–3.29, aOR: 1.75, 95% CI 0.93–3.29	tPA in patients with AIS with unknown symptom onset time or elapsed time from symptom onset >4.5 hours selected with advanced neuroimaging is associated with increased odds of complete recanalization and functional improvement at 3 months despite the increased sICH risk.

Trial/Paper	Population/ Aim	Arms	Design	Setting	Period	N. Patients	Main Results	Conclusion
Thomalla et al. (Lancet)[13]	Population: Adults with AIS receiving treatment with IV alteplase (0.9 mg/kg) either in the setting of unknown symptom onset time (wake-up strokes) or >4.5 hours from onset selected by advanced baseline neuroimaging with either CT or MRI Aim: To determine the safety and efficacy of alteplase among these patients when imaging biomarkers have identified salvageable tissue.	Individual-level meta-analyses **Intervention**: tPA (0.9 mg/kg) **Control**: No thrombolysis	Meta-analysis of individual patient data for trials published before Sept 21, 2020 (WAKE-UP, EXTEND, THAWS, and ECASS-4)	Same from Tsivgoulis et al (above).		843	• 429 IV tPA, 414 placebo • mRS 0-1: 47% tPA vs 39% placebo, aOR: 1.49, 95% CI: 1.10-2.03, p=0.011 • Better shift for tPA: acOR: 1.38, 95% CI: 1.05-1.80, p=0.019 • mRS 0-): adj. OR: 1.50, 95% CI: 1.06-2.12, p=0.022 • Higher deaths with alteplase: 6% vs 3%, p=0.040 • Higher sICH: 3% vs <1%, p=0.024	Among patients with stroke with unknown onset time with a DWI-FLAIR or perfusion mismatch, IV alteplase was associated with better functional outcomes at 90 days compared with placebo or standard care. The study authors observed a net benefit for all functional outcomes, despite an increased sICH risk.

Trial/Paper	Population/ Aim	Arms	Design	Setting	Period	N. Patients	Main Results	Conclusion
Campbell et al (2019 Lancet)[14]	Population: Adults with ischemic stroke more than 4.5 hours after stroke onset or wake-up stroke who had pretreatment imaging with CT perfusion or perfusion-diffusion MRI Aim: To determine the utility of perfusion imaging in the identification of patients with salvageable tissue at least 4.5 hours from the last known well or with symptoms on waking who benefit from thrombolysis	**Intervention**: (tPA) **Control**: No thrombolysis	Systematic review and meta-analysis of individual patient data (EXTEND, ECASS4-ExTEND, and EPITHET)	EPITHET: Alteplase given 3 to 6 hours after stroke onset among patients who have a mismatch in PWI and DWI		414	• 213 tPA vs 201 placebo • 90-day mRS 0-2: 36% vs 29%; aOR 1·86, (95% CI 1·15-2·99, p=0·011) • sICH: 5% vs <1%, aOR 9·7, 95% CI 1·23-76·55, p=0·031 • Mortality: 14% vs 9%; aOR 1·55, 0·81-2·96, p=0·66	Patients with ischemic stroke 4.5 to 9 hours from stroke onset or wake-up stroke with salvageable brain tissue who received treatment with alteplase demonstrated better functional outcomes compared with patients given placebo. The authors noted that the rate of sICH was higher with alteplase.

Trial/Paper	Population/ Aim	Arms	Design	Setting	Period	N. Patients	Main Results	Conclusion
Tenecteplase								
Katsanos (Stroke)[15]	Population: Patients with confirmed LVO who were randomly assigned to IV thrombolytic treatment with either tenecteplase or alteplase Aim: To compare the safety and efficacy outcomes between IV tenecteplase and IV alteplase for patients with acute ischemic stroke with LVOs.	**Intervention**: Tenecteplase at different doses **Control**: Alteplase at a standard dose of 0.9 mg/kg	Meta-analyses (ATTEST+Australian TNK, Australian TNK, EXTEND-IA TNK; NOR-TEST)	ATTEST: Pilot evaluation of tenecteplase compared with alteplase among patients with acute ischemic stroke currently eligible for intravenous alteplase treatment NOR-TEST is a multi-center PROBE TNK vs tPA (**Norway**)		433	• Primary outcome: Higher 90-day mRS 0-2 with TNK: OR 2.06 (95% CI, 1.15-3.69) • Higher odds of success recanal (OR, 3.05 [95%CI, 1.73–5.40] • Lower mortality with TNK: OR 0.93 (95%CI 0.31–2.80) • Lower sICH: OR 0.66 (0.19–2.23)	Patients with LVO who received IV thrombolysis with tenecteplase had significantly better recanalization and clinical outcomes than patients who received tPA.

Trial/Paper	Population/ Aim	Arms	Design	Setting	Period	N. Patients	Main Results	Conclusion
EXTEND-IA TNK Part 2 (JAMA)[16]	Population: Patients with ischemic stroke due to LVO of the intracranial ICA, MCA, or basilar artery who were eligible for intravenous thrombolysis and endovascular thrombectomy within 4.5 hours of stroke onset. Aim: To determine whether 0.40 mg/kg tenecteplase can safely improve reperfusion prior to endovascular thrombectomy vs 0.25 mg/kg of tenecteplase in large vessel occlusion ischemic stroke less than 4.5 hours after symptom onset.	**Intervention**: Tenecteplase at 0.40 mg/kg (maximum: 40 mg) given as a bolus before endovascular thrombectomy. **Control**: 0.25 mg/kg (maximum, 25 mg) given as a bolus before endovascular thrombectomy.	Randomized clinical trial using open-label treatment and blinded assessment	27 hospitals in Australia and 1 in New Zealand	December 2017 to July 2019 with follow-up until October 2019	300	• 150 [0.40]mg/kg vs 150 [0.25]mg/kg • Primary outcome: Substantial reperfusion 19.3% vs 19.3% –adj RR: 1.03 (95% CI, 0.66 – 1.61; P=0.89) • mRS 0-2: 59% vs 56%, adj RR: 1.08 (95% CI 0.90-1.29; P=0.40) • mTICI ≥2b: 82% in EVT group • Mortality: 17% vs 15%, adj RR: 1.27, 95% 0.77-2.11; P=0.35 • sICH (SITS MOST): 4.7% vs 1.3%, adj RR: 3.5 (0.74-16.62; P=0.12)	A dose of 0.40 mg/kg was not associated with significantly improved cerebral reperfusion before endovascular thrombectomy compared with 0.25 mg/kg tenecteplase in large vessel occlusion ischemic stroke.

Trial/Paper	Population/ Aim	Arms	Design	Setting	Period	N. Patients	Main Results	Conclusion
Intracerebral Hemorrhage								
Blood Pressure Management								
Moullaali T, (The Lancet)[17]	Population: Patients aged 19 to 99 years with spontaneous (non-traumatic) intracerebral hemorrhage and elevated systolic blood pressure (defined as 150–220 mm Hg in INTERACT2 and ≥180 mm Hg in ATACH-II), without a clear indication or contraindication to treatment. Aim: To evaluate the effect of blood pressure reduction and variability on functional and safety outcomes after intracerebral hemorrhage.	Individual patient-level meta-analyses of INTERACT 2 and ATACH 2 Both had intensive vs standard guidelines, and suggested reduction in BP as treatment arms. The meta-analysis assesses overall effect of reduction in BP across both arms combined.	BP reduction measures **Achieved systolic BP:** the mean of the systolic BP measurements at 5 time points (every 15 min within the first hour and then at 6 hours, 12 hours, 18 hours, and 24 hours.) **Variability:** The SD of the systolic BP measures obtained at 5 time points between 1 hour and 24 hours **Magnitude**: Difference between SBP at randomization and lowest attained SBP within 1 hour	INTERACT2: International, open label, blinded endpoint assessment trial with >100 centers. Trial assess intensive BP lowering (<140 mmHg) vs standard management (<180 mmHg). Intervention stopped at SBP <130 mmHg. Any locally available treatment usable. ATTACH-II international trial among patients with ICH who are treated within 4.5 hours of symptom onset. Intensive SBP reduction (110-139) vs Guideline suggested (140-179) reduction using IV nicardipine.	INTERACT – II: 2008-2012 ATACH-II: 2011-2015	3829, INTERACT-II: 2829; ATACH II: 1000	**Mean SBP across 24 hours:** 147 +/-15 mmHg **Magnitude of reduction in first hour:** 29 +/- 22 mmHg **Mean SBP variability:** 14 +/- 8 mmHg **Higher Mean SBP across 5 time points in 24 hours was associated with worse functional outcomes** (mRS distribution) – for every 10 mmHg acOR: 0·90 [95% CI 0·87–0·94], p<0·0001. **Also, other worse outcomes** (good outcome – mRS 0-3, functional independence, mortality, Neuro deterioration, hematoma expansion and 90-day SAEs). **Higher SBP variability was associated with worse outcomes** good outcome – mRS 0-3 and functional independence. **Also, other worse outcomes** (mortality, neurodeterioration, hematoma expansion and 90-day SAEs); **mRS distribution failed proportional odds assumption** Magnitude of SBP reduction – not significantly associated with any functional or safety outcomes. **mRS distribution failed proportional odds assumption**	Lower **mean SBP** was associated with better functional and safety outcomes. Higher **SBP variability** was associated with worse outcomes. U-shaped relationships observed in **SBP variability and magnitude of SBP reduction in first hour** with several outcomes.

Trial/Paper	Population/ Aim	Treatment Assignment	Design	Setting	Period	N. Patients	Main Results	Conclusion
Neuroprotection								
ESCAPE-NA1[18]	**Population:** Adults (aged at least 18 years) with NIHSS >5, ASPECTS ≥5 on CT, proximal LVO (ICA/M1), and ≥50% filling of MCA pial arterial circulation on multiphase CTA with functional independence (Barthel Index score >90) at baseline, presenting within 12 hours of last seen well. **Aim:** To evaluate whether nerinetide, in addition to usual care with IV alteplase, is associated with improved outcomes among patients with EVT.	**Treatment arm:** Nerinetide 2.6 mg/kg, up to 270 mg using IV bolus over 10 minutes **Placebo arm:** Normal saline using IV bolus	International, multicenter, randomized, double-blind, placebo-controlled, parallel-group, single-dose trial **Primary outcome:** mRS score of 0-2 at 90 days	48 centers in Canada, USA, Germany, Australia, South Korea, Sweden, Ireland and UK	March 2017 to Aug 2019	1105 patients	• 337 (61·4%) of 549 patients with nerinetide and 329 (59·2%) of 556 with placebo achieved the primary outcome (adjusted risk ratio 1·04, 95% CI 0·96–1·14; p=0·35) • No difference in secondary outcomes, including mortality, excellent outcomes, infarct volume • Treatment effect modification observed with alteplase (mRS 0-2 at 90d: No alteplase - adjusted RR: 1·18, 95% CI 1·01 to 1·38; Alteplase – adjusted RR: 0.97, 95% CI 0.87-1.08.	Nerinetide did not demonstrate neuroprotection among all patients with ischemic stroke due to large vessel occlusion who received treatment with EVT plus usual stroke treatment with or without intravenous alteplase. The authors observed a treatment effect among patients who did not receive alteplase.

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