Online July 12, 2023
Journal of Neuroendovascular Therapy 2023; 17: 263–271 DOI: 10.5797/jnet.ra.2023-0035

Review Article

A Review on Adjunctive Therapies for Endovascular Treatment in Acute Ischemic Stroke

Mayank Goyal,[1] Leon A. Rinkel,[1,2] and Johanna M. Ospel[1]

Endovascular treatment (EVT) has revolutionized the management of acute ischemic stroke (AIS), but almost half of patients undergoing EVT do not achieve a good outcome. Adjunctive therapies have been proposed to improve the outcomes of EVT in AIS. This review aims to summarize the current evidence on the use of adjunctive therapies in EVT for AIS, including antithrombotic agents, intra-arterial thrombolytics, cerebroprotective agents, normobaric oxygen, and hypothermia. Several adjunctive therapies have shown promise in improving the outcomes of EVT in AIS, but phase 3 clinical trials are needed to establish clinical efficacy. We summarize the advantages and disadvantages of adjunctive EVT treatments and outline the challenges that each of these therapies will face before being adopted in clinical practice.

Keywords acute ischemic stroke, endovascular therapy, mechanical thrombectomy, intra-arterial thrombolysis, neuroprotection

Introduction

Acute ischemic stroke (AIS) is often caused by a blood clot, which occludes a cerebral artery and thereby interrupts blood supply to the brain parenchyma. AIS, particularly when caused by a large vessel occlusion (LVO), is a devastating disease and results in high morbidity and mortality.[1)] Until 2015, the only guideline-based treatment option for LVO–AIS was intravenous thrombolysis via administration of alteplase, a tissue plasminogen activator that dissolves blood clots.[2)] However, the efficacy of intravenous alteplase in LVO and medium vessel occlusion (MeVO) is low, and early recanalization is achieved in less than half of LVO patients.[3)] In 2015, endovascular treatment (EVT), that is, mechanical clot removal, has become standard of care for AIS due to LVO,[4,5)] and currently ongoing trials aim to prove its benefit in MeVO–AIS as well. Although EVT has dramatically improved AIS outcomes, with a number needed to treat in LVO–AIS as low as 2.6,[4)] data from randomized trials suggest that 40%–50% of LVO patients do not achieve a good outcome and 10%–20% die within 3 months.[4,6)] Outcomes in the "real world" outside clinical trial settings are likely even worse.

Moreover, even patients who have near-complete reperfusion following EVT according to the expanded Thrombolysis in Cerebral Infarction (eTICI) scale may have significant disability.[7)] The reasons for this apparent discrepancy between technical and clinical EVT outcomes is not well understood, and may be related to late reperfusion (after irreversible damage has already occurred), microvascular obstruction that is not visible on crude macroscopic scales such as Thrombolysis in Cerebral Infarction (TICI), reperfusion injury, and reperfusion-induced hemorrhage.

Thus, there is substantial room for improvement of EVT outcomes, and numerous adjunctive therapies are currently being investigated to enhance EVT effect and increase good outcome rates after EVT. In this review, we will outline promising adjunctive treatments that have the potential to improve outcomes of patients undergoing EVT, discuss potential challenges associated with these new treatments, and provide a framework for how such adjunctive treatment strategies could be adopted in clinical practice.

[1]*Department of Diagnostic Imaging and Clinical Neurosciences, Foothills Medical Center, University of Calgary, Calgary, AB, Canada*
[2]*Department of Neurology, Amsterdam University Medical Center, Amsterdam, the Netherlands*

Received: May 9, 2023; Accepted: May 24, 2023
Corresponding author: Mayank Goyal. Departments of Radiology and Clinical Neurosciences, Foothills Medical Centre, University of Calgary, 1403, 29th St. NW, Calgary, AB T2N2T9, Canada
Email: mgoyal@ucalgary.ca

Of note, while intravenous thrombolysis could be seen as an adjunctive EVT treatment in a broader sense, it has been used long before EVT, and excellent reviews on the role of intravenous thrombolysis in addition to EVT exist.[8] Thus, we will refrain from discussing the role of concomitant intravenous thrombolysis in the setting of EVT.

What are Potential Mechanisms of Action for Adjunctive Therapies in the EVT Setting?

EVT improves AIS outcomes by recanalizing the occluded blood vessel, which leads to restoration of blood flow in the previously ischemic brain tissue. However, EVT cannot always salvage the ischemic tissue because reperfusion may be incomplete, may occur too late, may result in complications (eg, iatrogenic infarcts through thrombus fragmentation, embolization of thrombi that form around catheter and wire tips or vessel perforation/rupture), or the tissue may sustain damage from detrimental changes that occur after reperfusion (so-called "reperfusion injury").

Each of these four points are potential target mechanisms for adjunctive treatments (**Table 1** and **Fig. 1**). Incomplete reperfusion could be mitigated by "reperfusion enhancers"; ie, drugs that are injected into the arterial bed after macroscopic reperfusion has been achieved to dissolve remaining microthrombi. Reperfusion occurring "too late" could be tackled by bridging cerebroprotectants, which prolong ischemia tolerance of brain tissue and thereby "slow down the clock." Procedural complications can only be avoided to a certain degree, but it has been hypothesized that antithrombotic medication may reduce thrombus formation around intravascular devices and could thereby in theory lower the periprocedural complication rate. Reperfusion injury is an under-researched and under-recognized phenomenon, but ongoing research suggests that there are drugs that could decrease reperfusion injury post EVT.

Assessing Reperfusion Status

Our current assessment of reperfusion status is an imperfect method. Quality of reperfusion in the middle cerebral artery territory following EVT is measured using the eTICI, and near-complete reperfusion (eTICI 2c/3, ie, >90% vessel opacification in the affected territory) is the goal when performing EVT.[9] In recent randomized controlled trials, macroscopic near-complete reperfusion (eTICI 2c-3) was achieved in less than half of all LVO patients.[10] However even in case of macroscopic near-complete reperfusion (eTICI 2c-3 on the final intracranial angiogram), tissue-level reperfusion may not be completely re-established. In fact, some argue that the eTICI score does at least partially represent recanalization, rather than true reperfusion at the tissue level.[11–14] The main reason for impaired tissue-level reperfusion despite near-complete macroscopic (eTICI 2c-3) reperfusion is impaired microcirculatory reperfusion (IMR). IMR is caused by microthrombi, neutrophil extracellular traps (NETs), astrocyte swelling, and pericyte constriction.[15] Microvascular obstruction has long been known as a poor prognostic marker in myocardial infarction,[16] and it is becoming increasingly evident that it is also an important driver of tissue damage in AIS. Additionally, eTICI does not provide any information on tissue-specific reperfusion. While macrovascular successful recanalization may be achieved on DSA during EVT, perforating arteries supplying the basal ganglia can remain occluded. The eloquence of this brain region dictates that occlusions of these small arteries have a strong adverse effect on the functional outcome. In addition, previous research showed that loss of cortical white matter has a more severe impact on poststroke functional status than cortical gray matter, yet tissue-specific fate cannot be assessed on eTICI.

Assessing final infarct volumes on follow-up imaging after stroke can overcome some the problems associated with eTICI as it allows for a more comprehensive assessment of tissue-specific reperfusion. However, it has its own limitations. First, it is most reliably assessed on MRI that may have limited availability and can be costly and time consuming. Second, it may be prone to measurement error: the infarct borders are often not clearly visible on non-contrast head CT, and even on diffusion weighted MRI – the "gold standard" for infarct assessment – there is often a subtle, gradual transition from clearly infarcted, diffusion-weighted imaging-hyperintense to unaffected tissue, and it can be hard to accurately delineate the infarct border. Movement and partial volume artifacts are additional limitations, the latter one being of particular relevance in small infarcts with a gyriform, dendritic pattern and a high surface area to volume ratio.[17] Furthermore, infarcts grow even after 24 hours, so that a 24-hour scan may not necessarily reflect the true final infarct volume. Finally, by the time follow-up imaging is acquired, the time window for therapeutic opportunities may have already passed. However, novel innovations allow for short MR acquisition times with true reflection of microcirculation disturbances and correlate with tissue necrosis.[18–20]

Table 1 Common reasons for not achieving a good outcome after EVT and potential adjunctive therapy solutions

Reason	Explanation	Adjunctive therapy solution	Example
Late reperfusion	In AIS, ischemic tissue continues to progress to infarction until reperfusion is achieved. If reperfusion occurs too late, all the ischemic tissue has already infarcted, and there is nothing left to salvage	Early administration (eg, ambulance setting) of bridging cerebroprotectants that prolong ischemia tolerance of the brain tissue and can extend the survival of ischemic tissue, thereby expanding the therapeutic window for EVT	Intravenous Nerinetide,*[,10] intra-arterial, intranasal, or external cooling*[,39]
Incomplete reperfusion	Incomplete reperfusion of the brain tissue downstream to the occlusion, due to incomplete removal of the thrombus (parts of the thrombus remain at the site of occlusion), thrombus migration, or fragmentation and embolization to distal vessel branches	Intra-arterial injection of "reperfusion enhancers" can dissolve small distal thrombi and thereby improve patient outcomes. However, for heparin and aspirin, an increased hemorrhage risk was shown.[30]	Intra-arterial urokinase,[22] alteplase,[21] or Tenecteplase (clinicaltrials.gov: NCT05684172), intravenous heparin[30]
Reperfusion injury	Tissue damage that occurs in previously ischemic tissue when oxygen is re-introduced through reperfusion, resulting in ROS formation and "oxidative stress", as well as glutamate-induced excitotoxicity[49,50]	Molecules that interfere with glutamate receptors and inhibit excitotoxic and pro-inflammatory signalling pathways in brain tissue could in theory reduce reperfusion injury. However, no such drug is approved for use in human AIS yet[51]	Veliparib (third-generation Parthanatos pathway inhibitor)*[,52]
Blood–brain barrier breakdown	Extensive ischemia can damage the blood–brain barrier, resulting in edematous changes of the brain parenchyma, hemorrhagic infarction, or in extreme cases, frank mass hemorrhage	Blood–brain barrier stabilizers could prevent/reduce blood–brain barrier damage and the subsequent edema and hemorrhage. However, currently there is no blood–brain barrier stabilizer available in clinical routine yet	DI-3-n-butylphthalide (not used in clinical routine yet)[53]
Procedural complications	Although the rate of EVT-related complications is generally low, procedural complications that can result in poor post EVT outcomes include vessel perforation with subsequent hemorrhage, dissection, iatrogenic infarcts, and thrombotic complications due to thrombus formation around intravascular catheters and devices	Not all procedural complications can be treated effectively, and prevention is by far the better option. However, the risk of thrombus formation around catheters and devices can in theory be reduced by antithrombotic agents. However, for intravenous heparin and aspirin, an increased hemorrhage risk was shown.[30]	Aspirin, clopidogrel,[54] intravenous heparin[30]

*Not yet available for routine clinical care. AIS: acute ischemic stroke; EVT: endovascular treatment; ROS: reactive oxygen species

Intra-Arterial Thrombolytics

Adjunctive intra-arterial thrombolytics may be an effective method to improve post-EVT outcomes in both patients with and without macroscopic near-complete reperfusion. Indeed, the randomized CHOICE trial showed benefit of adjunctive intra-arterial alteplase in patients with successful reperfusion (eTICI 2b3),[21] which the authors believed to be a result of improved microcirculatory reperfusion. Another cohort study showed that intra-arterial urokinase in EVT patients with failed or incomplete reperfusion improves clinical outcomes, whereby these changes were not explained by improved post-infusion eTICI scale, again suggesting improvements in previously impaired microcirculation that are not adequately captured by eTICI.[22] The ongoing TECNO trial (clinicaltrials.gov: NCT05499832) investigates the safety and efficacy of adjunctive intra-arterial tenecteplase in EVT patients with non-complete reperfusion.

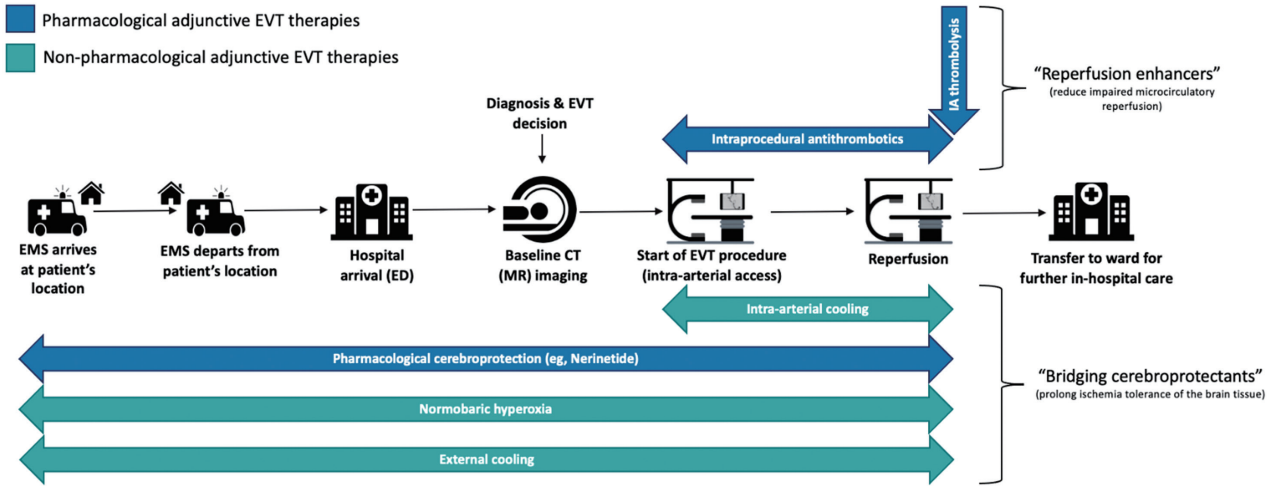

Fig. 1 Adjunctive EVT treatments and timing of administration during the acute stroke workflow. Reperfusion enhancers are pharmacological adjunctive EVT treatments that are applied either intravenously or intra-arterially in the periprocedural time period. Since they carry a significant risk of hemorrhagic side effects, they cannot be administered prior to hospital arrival. Cooling is a non-pharmacological EVT adjunct that prolongs ischemia tolerance of the brain by slowing down the metabolic rate of the brain tissue. Intra-arterial cooling can only be applied during EVT since it requires intra-arterial access, while external cooling can be applied as early as in the pre-hospital setting. Normobaric hyperoxia is another non-pharmacological EVT adjunct that improves ischemia tolerance of the brain by increasing tissue oxygen supply. It too can be administered early on at the pre-hospital stage. The same is true for some pharmacological cerebroprotectants. Nerinetide, for example, is a bridging cerebroprotectant with an excellent safety profile that could potentially be administered in the field as well. EVT: endovascular treatment

While intra-arterial thrombolytics are formally considered off-label treatment, they are nevertheless frequently used as rescue strategies in clinical practice when an occlusion cannot be reached with stent retrievers or aspiration catheters, or when performing mechanical retrieval maneuvers is considered too risky.

One of the potential drawbacks for intra-arterial thrombolytics is that it is unknown what happens when it is administered in patients who only have truly infarcted brain tissue. Reperfusion of truly infarcted tissue likely does not yield any benefit as there is nothing left to salvage, while it increases the probability of hemorrhagic transformation of the infarcted region. The question when there is still enough tissue to salvage a topic of ongoing debate with recent trials showing benefit of recanalization even in patients with large infarcted areas and relatively little salvageable tissue.[23–25]

Antithrombotics

Another proposed method to improve reperfusion and outcomes has been the use of systemic administration of antithrombotic as an adjunctive therapy.[26] The rationale behind this was that IMR, which has a negative effect on tissue recovery following ischemia, could be reduced by systemic antithrombotic treatment[27–29]; platelet inhibitors, such as aspirin, may decrease the number of microthrombi and unfractionated heparin could dissolve thrombi with NETs while simultaneously inactivating thrombin to prevent fibrin formation. The MR CLEAN–MED trial assessed whether administration of aspirin, unfractionated heparin, or both during EVT increased functional outcome using a 2 × 3 factorial design in 15 centres in the Netherlands.[30] The trial was stopped early for safety concerns as the risk of symptomatic intracranial haemorrhage was higher in patients allocated to receive aspirin and in patients allocated to unfractionated heparin. Another antiplatelet drug, tirofiban, was recently shown to not improve outcome when given before EVT.[31] As such, there is no evidence to suggest benefit of adjunctive antithrombotics during EVT, and aspirin, unfractionated heparin, and tirofiban should not be used as an adjuvant therapy to EVT based on current evidence.

Pharmacological Cerebroprotection

Numerous adjunctive cerebroprotective drugs are currently in development, and they tackle different ischemic tissue damage mechanisms.[32] Several agents are currently evaluated in the preclinical setting within the Stroke PreClinical Assessment Network.[33] Nerinetide is perhaps the compound that is closest to being used in clinical routine. The eicosapeptide inhibits postsynpatic density 95 protein–protein interactions that result in excitotoxic cell death in acute ischaemia.[34] Since the signalling pathways that Nerinetide interferes with occur mainly prior to reperfusion, Nerinetide can be considered a bridging cerebroprotectant, ie, a drug that prolongs ischemia tolerance of the brain

until reperfusion is achieved via EVT. In the ESCAPE-NA1 trial, a randomized controlled phase-3 trial, Nerinetide was associated with improved outcomes in patients who did not receive intravenous alteplase.[10] In patients receiving alteplase, no such benefit was seen, most likely due to a biological interaction, whereby alteplase cleavage products inactivate Nerinetide. The ongoing ESCAPE-NEXT trial aims to confirm the results from the no-alteplase stratum (clinicaltrials.gov: NCT04462536). Besides Nerinetide, there are also other promising compounds that are currently tested in phase 2b trials, such as RNS-60 (clinicaltrials.gov: NCT04693715) or ApTOLL (NCT04734548). The ApTOLL trial was phase Ib/IIa randomized trial that investigated the safety, pharmacokinetics, and biological effect of ApTOLL, a Toll-like receptor 4 antagonist in human AIS patients undergoing EVT within 6 hours from symptom onset.[35] The trial showed that higher ApTOLL doses substantially reduced death rates, along with a dramatic reduction in infarct volume, while lower ApTOLL doses resulted in similar outcomes compared to placebo. Importantly, as opposed to Nerinetide, no interaction with intravenous thrombolytics was observed.[36] As such, ApTOLL is another promising agent that could soon complement the EVT treatment regimen.

Cooling/Hypothermia

The concept behind adjunctive cooling strategies in EVT is that hypothermia reduces the metabolic rate of brain tissue. Therapeutic hypothermia is an established treatment for cardiac arrest and hypoxic–ischemic encephalopathy in newborns but is not routinely used in AIS.[37] The main reason is that intra-arterial cooling as a bridging cerebroprotectant can only be applied for a short time – that is, the time between establishing arterial access and reperfusion. In order to place a cooling catheter, reperfusion may even get delayed. Previous studies showed that short intra-arterial cooling periods of 10 minutes or less do not seem to influence the oxygen extraction fraction, which is a proxy for the metabolic rate,[38] suggesting that such a short cooling period does not alter brain metabolism in a meaningful way.[39]

Systemic cooling, for example through cooling collars or cooling pads that are externally applied, does not require intra-arterial access and could be applied as early as in the ambulance. However, systemic cooling has substantial systemic side effects, such as bradycardia, electrolyte imbalances and acidosis, and increased risk of infection.[37] Moreover, a previous trial on systemic cooling of stroke patients showed that feasibility is a major concern.[40] The trial was able to include only 98 of the originally intended 1500 patients over a period of 6 years, mainly due to the complexity of cooling awake patients with ischaemic stroke. Therefore, it seems unlikely that systemic cooling will be a widely applicable treatment for patients with AIS.

While safety of intra-arterial cooling in human AIS has been proven,[39] there are also no trials that have proven that it is beneficial. Another promising alternative option is local cooling using intranasal catheters, which has been proven to be safe in patients with out-of-hospital cardiac arrest[41] and brain injury,[42] although efficacy data are hitherto lacking.

Normobaric Hyperoxia

The main problem in AIS is lack of oxygen supply in the ischemic tissue with decreased interstitial partial oxygen pressure in the affected areas.[43] Increasing oxygen supply in the ischemic tissue could in theory diminish the detrimental effects of the vessel occlusion and slow down infarct progression until reperfusion is achieved (bridging cerebroprotection). Oxygen is a small hydrophobic molecule that can easily cross the blood–brain barrier. Thus, adjunctive hyperoxia (eg, 100% oxygen inhalation through a face mask) could increase the interstitial partial oxygen pressure in the ischemic tissue until reperfusion is achieved via EVT. In addition, it could also unfold beneficial effects in the post-reperfusion period by reducing harmful effects of persisting impaired microcirculatory reperfusion after macroscopic near-complete (eTICI 2c-3) reperfusion. Indeed, a recent randomized trial has shown improved clinical outcomes and reduced infarct volumes in EVT patients with adjunctive periprocedural normobaric hyperoxia.[44] At the time being, normobaric hyperoxia is not routinely used in clinical care, but once its safety and efficacy have been confirmed in additional studies, hyperoxia could soon become standard of care for EVT patients. Hemoglobin-based oxygen carriers are another promising method to increase oxygen supply of the brain and are currently tested in the human AIS setting in an ongoing phase 1 trial.[45]

The current review has focussed specifically on adjuvant therapies for EVT to improve outcome after stroke. However, there are many events occurring after EVT that can negatively influence the functional outcome at 90 days and thus confound the association between outcome and post-EVT reperfusion status. Factors such infections, recurrent strokes, and inadequate stroke rehabilitation play

Table 2 Adjunctive therapies in EVT

	Challenges	Strengths	Ongoing phase 3 RCTs*	Likelihood of adoption in clinical care
Normobaric hyperoxia	Limited data supporting efficacy. The potential for oxygen toxicity, lack of consensus on optimal oxygen dosing	Feasible to administer and measure, low costs, widely available, generally safe. Phase 2 trial showed benefit in reduction of final infarct volume and improved functional outcome	None	+
Pharmacological cerebroprotection	Many cerebroprotective agents have failed to show benefit in phase 3 trials despite promising results of earlier phase trials. Lack of clear understanding of the mechanisms of action for some promising agents	Many agents currently being investigated showed promising results in early phase trials. Evidence of effect in subgroup analysis of phase 3 trial for Nerenitide	ESCAPE-NEXT NCT04462536 RODIN NCT05041010 MIST-B NCT05512910 TASTE-2 NCT05249920 Cerebrolysin NCT05124353	++
Cooling/ hypothermia	Systemic cooling seems unfeasible due to the complexity of the intervention. Intra-arterial cooling may be more feasible, yet has its own challenges: there is no clear target for temperature reduction and measurement of brain temperature may be difficult	Safety of intra-arterial cooling shown in phase 2 trial	None	–
Intra-arterial thrombolytics	Unclear whether beneficial in patients with successful reperfusion, without successful reperfusion or both. sICH is a potential concern	Phase 2b trial showed benefit of alteplase but was terminated early. Several ongoing phase 3 trials	TECNO NCT05499832 CHOICE 2 NCT05797792 ATTENTION IA NCT05684172	+++

*Limited to trials specifically focussing on EVT for AIS. We did not add antithrombotics to the table since currently no promising agents appear to be available, although this may change in the future. AIS: acute ischemic stroke; EVT: endovascular treatment; RCT: randomized controlled trial; sICH: symptomatic intracranial hemorrhage

an important role in explaining why some patients have poor outcome despite successful reperfusion.[46,47] Therefore, attention should be given to the entire chain of stroke care to improve patient outcomes.

Adjunctive Therapies in EVT – Which Challenges are Yet to be Overcome?

Why is it that none of the above promising adjunctive treatments are established in routine AIS care yet? The answer is that each of these strategies has their own logistic challenges and complication risks.

Table 2 provides an overview of the unique challenges, strengths, ongoing phase 3 trials, and the likelihood of the treatment being adopted in clinical routine for each adjunctive treatment.

A Look Forward

More data from phase 3 randomized controlled trials are needed to establish any of these various promising adjuvant therapies in clinical practice. Historically speaking, there is a stepwise efficacy decline of treatments from early phase studies to phase 3 clinical trials.[48] Undoubtedly, many of potential adjuvant EVT therapies have shown

promising results in early stage 2 trials, but how many of these treatments will finally make it into clinical practice remains to be seen. For some of them, phase 3 trials are already ongoing or have even completed patient inclusion. Of particular interest are the results of the ESCAPE-NEXT trial, which are expected in 2023. Moreover, the ongoing phase 3 trials will provide an answer whether intra-arterial thrombolytics should be routinely administered during EVT. Overall, the use of adjunctive therapies in conjunction with EVT is a rapidly evolving field with significant potential to improve outcomes for patients with AIS. With continued research and innovation, adjunctive therapies for EVT may become a standard part of the management of AIS in the near future.

Disclosure Statement

The authors have nothing to disclose.

References

1) Ospel JM, Holodinsky JK, Goyal M. Management of acute ischemic stroke due to large-vessel occlusion: JACC focus seminar. *J Am Coll Cardiol* 2020; 75: 1832–1843.
2) National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995; 333: 1581–1587.
3) Ospel JM, Singh N, Almekhlafi MA, et al. Early recanalization with alteplase in stroke because of large vessel occlusion in the ESCAPE trial. *Stroke* 2021; 52: 304–307.
4) Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet* 2016; 387: 1723–1731.
5) Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2018; 49: e46–e110.
6) Heiss WD, Rosner G. Functional recovery of cortical neurons as related to degree and duration of ischemia. *Ann Neurol* 1983; 14: 294–301.
7) Olivot J-M, Heit JJ, Mazighi M, et al. What predicts poor outcome after successful thrombectomy in early time window? *J Neurointerv Surg* 2022; 14: 1051–1055.
8) Campbell BCV, Kappelhof M, Fischer U. Role of intravenous thrombolytics prior to endovascular thrombectomy. *Stroke* 2022; 53: 2085–2092.
9) Almekhlafi MA, Mishra S, Desai JA, et al. Not all "successful" angiographic reperfusion patients are an equal validation of a modified TICI scoring system. *Interv Neuroradiol* 2014; 20: 21–27.
10) Hill MD, Goyal M, Menon BK, et al. Efficacy and safety of nerinetide for the treatment of acute ischaemic stroke (ESCAPE-NA1): a multicentre, double-blind, randomised controlled trial. *Lancet* 2020; 395: 878–887.
11) Goyal M, Fargen KM, Turk AS, et al. 2C or not 2C: defining an improved revascularization grading scale and the need for standardization of angiography outcomes in stroke trials. *J Neurointerv Surg* 2014; 6: 83–86.
12) Jayaraman MV, Grossberg JA, Meisel KM, et al. The clinical and radiographic importance of distinguishing partial from near-complete reperfusion following intra-arterial stroke therapy. *AJNR Am J Neuroradiol* 2013; 34: 135–139.
13) Tung EL, McTaggart RA, Baird GL, et al. Rethinking thrombolysis in cerebral infarction 2b: which thrombolysis in cerebral infarction scales best define near complete recanalization in the modern thrombectomy era? *Stroke* 2017; 48: 2488–2493.
14) Ospel J, Rex N, Kandregula S, et al. The vessel has been recanalized: now what? *Neurotherapeutics* 2023; 20: 679–692.
15) Ng FC, Coulton B, Chambers B, et al. Persistently elevated microvascular resistance postrecanalization. *Stroke* 2018; 49: 2512–2515.
16) Wu KC, Zerhouni EA, Judd RM, et al. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. *Circulation* 1998; 97: 765–772.
17) Ospel JM, Jaffray A, Schulze-Zachau V, et al. Spatial resolution and the magnitude of infarct volume measurement error in DWI in acute ischemic stroke. *AJNR Am J Neuroradiol* 2020; 41: 792–797.
18) Engedal TS, Hjort N, Hougaard KD, et al. Transit time homogenization in ischemic stroke - a novel biomarker of penumbral microvascular failure? *J Cereb Blood Flow Metab* 2018; 38: 2006–2020.
19) Hansen MB, Tietze A, Kalpathy-Cramer J, et al. Reliable estimation of microvascular flow patterns in patients with disrupted blood-brain barrier using dynamic susceptibility contrast MRI. *J Magn Reson Imaging* 2017; 46: 537–549.
20) Fladt J, Guo J, Specht J, et al. Abstract 119: the effect of neuroprotectant NA1 on early infarct growth following endovascular therapy: the REPERFUSE-NA1 study. *Stroke* 2022; 53(Supp_1): A119.
21) Renú A, Millán M, San Román L, et al. Effect of intra-arterial alteplase vs placebo following successful thrombectomy on functional outcomes in patients with large vessel occlusion acute ischemic stroke: the CHOICE randomized clinical trial. *JAMA* 2022; 327: 826–835.

22) Kaesmacher J, Bellwald S, Dobrocky T, et al. Safety and efficacy of intra-arterial urokinase after failed, unsuccessful, or incomplete mechanical thrombectomy in anterior circulation large-vessel occlusion Stroke. *JAMA Neurol* 2020; 77: 318–326.
23) Yoshimura S, Sakai N, Yamagami H, et al. Endovascular therapy for acute stroke with a large ischemic region. *N Engl J Med* 2022; 386: 1303–1313.
24) Sarraj A, Hassan AE, Abraham MG, et al. Trial of endovascular thrombectomy for large ischemic strokes. *N Engl J Med* 2023; 388: 1259–1271.
25) Uchida K, Shindo S, Yoshimura S, et al. Association between Alberta stroke program early computed tomography score and efficacy and safety outcomes with endovascular therapy in patients with stroke from large-vessel occlusion: a secondary analysis of the recovery by endovascular salvage for cerebral ultra-acute embolism-Japan Large Ischemic Core Trial (RESCUE-Japan LIMIT). *JAMA Neurol* 2022; 79: 1260–1266.
26) Fransen PSS, Berkhemer OA, Lingsma HF, et al. Time to reperfusion and treatment effect for acute ischemic stroke. *JAMA Neurol* 2016; 73: 190–196.
27) Ames A 3rd, Wright RL, Kowada M, et al. Cerebral ischemia. II. The no-reflow phenomenon. *Am J Pathol* 1968; 52: 437–453.
28) Bekkers SC, Yazdani SK, Virmani R, et al. Microvascular obstruction: underlying pathophysiology and clinical diagnosis. *J Am Coll Cardiol* 2010; 55: 1649–1660.
29) Buchweitz-Milton E, Weiss HR. Perfused microvascular morphometry during middle cerebral artery occlusion. *Am J Physiol* 1988; 255: H623–H628.
30) van der Steen W, van de Graaf RA, Chalos V, et al. Safety and efficacy of aspirin, unfractionated heparin, both, or neither during endovascular stroke treatment (MR CLEAN-MED): an open-label, multicentre, randomised controlled trial. *Lancet* 2022; 399: 1059–1069.
31) RESCUE BT Trial Investigators. Effect of intravenous tirofiban vs placebo before endovascular thrombectomy on functional outcomes in large vessel occlusion stroke: the RESCUE BT randomized clinical trial. *JAMA* 2022; 328: 543–553.
32) Fisher M, Savitz SI. Pharmacological brain cytoprotection in acute ischaemic stroke - renewed hope in the reperfusion era. *Nat Rev Neurol* 2022; 18: 193–202.
33) SPAN. Stroke Pre-Clinical Assessment Network (SPAN). Published 2022. (Accessed Nov 6, 2022) https://spannetwork.org/Interventions
34) Aarts M, Liu Y, Liu L, et al. Treatment of ischemic brain damage by perturbing NMDA receptor-PSD-95 protein interactions. *Science* 2002; 298: 846–850.
35) Hernández-Jiménez M, Abad-Santos F, Cotgreave I, et al. APRIL: a double-blind, placebo-controlled, randomized, Phase Ib/IIa clinical study of ApTOLL for the treatment of acute ischemic stroke. *Front Neurol* 2023; 14: 1127585.
36) Neuronews. Neuroprotective agent linked to reduced death and disability in ischaemic stroke trial. *Neuronews*. Published 2023. (Accessed May 22, 2023) https://neuronewsinternational.com/aptoll-neuroprotective-agent-april-trial-isc-2023/
37) Wu L, Huber M, Wu D, et al. Intra-arterial cold saline infusion in stroke: historical evolution and future prospects. *Aging Dis* 2020; 11: 1527–1536.
38) Choi JH, Marshall RS, Neimark MA, et al. Selective brain cooling with endovascular intracarotid infusion of cold saline: a pilot feasibility study. *AJNR Am J Neuroradiol* 2010; 31: 928–934.
39) Chen J, Liu L, Zhang H, et al. Endovascular hypothermia in acute ischemic stroke. *Stroke* 2016; 47: 1933–1935.
40) van der Worp HB, Macleod MR, Bath PM, et al. Therapeutic hypothermia for acute ischaemic stroke. Results of a European multicentre, randomised, phase III clinical trial. *Eur Stroke J* 2019; 4: 254–262.
41) Nordberg P, Taccone FS, Truhlar A, et al. Effect of transnasal evaporative intra-arrest cooling on functional neurologic outcome in out-of-hospital cardiac arrest: the PRINCESS randomized clinical trial. *JAMA* 2019; 321: 1677–1685.
42) Abou-Chebl A, Sung G, Barbut D, et al. Local brain temperature reduction through intranasal cooling with the RhinoChill device. *Stroke* 2011; 42: 2164–2169.
43) Shen J, Sood R, Weaver J, et al. Direct visualization of mouse brain oxygen distribution by electron paramagnetic resonance imaging: application to focal cerebral ischemia. *J Cereb Blood Flow Metab* 2009; 29: 1695–1703.
44) Li W, Qi Z, Ma Q, et al. Normobaric hyperoxia combined with endovascular treatment for patients with acute ischemic stroke: a randomized controlled clinical trial. *Neurology* 2022; 99: e824–e834.
45) Linfante I, Hanel R, Reshi R, et al. Abstract number - 8: HEMERA 1 carboxyhemoglobin oxygen delivery for revascularization in acute stroke: phase 1 clinical trial. *Stroke Vasc Intervent Neurol* 2023; 3: e12443.
46) Ganesh A, Ospel JM, Menon BK, et al. Assessment of discrepancies between follow-up infarct volume and 90-day outcomes among patients with ischemic stroke who received endovascular therapy. *JAMA Netw Open* 2021; 4: e2132376.
47) Ospel JM, Ganesh A, Kappelhof M, et al. Evaluating outcome prediction models in endovascular stroke treatment using baseline, treatment, and posttreatment variables. *Stroke Vasc Intervent Neurol* 2021; 1: e000167.
48) Schmidt-Pogoda A, Bonberg N, Koecke MHM, et al. Why most acute stroke studies are positive in animals but not in patients: a systematic comparison of preclinical, early phase, and phase 3 clinical trials of neuroprotective agents. *Ann Neurol* 2020; 87: 40–51.

49) Nour M, Scalzo F, Liebeskind DS. Ischemia-reperfusion injury in stroke. *Interv Neurol* 2013; 1: 185–199.
50) Goyal M, McTaggart R, Ospel JM, et al. How can imaging in acute ischemic stroke help us to understand tissue fate in the era of endovascular treatment and cerebroprotection? *Neuroradiology* 2022; 64: 1697–1707.
51) Lyden PD. Cerebroprotection for acute ischemic stroke: looking ahead. *Stroke* 2021; 52: 3033–3044.
52) Koehler RC, Dawson VL, Dawson TM. Targeting parthanatos in ischemic stroke. *Front Neurol* 2021; 12: 662034.
53) Nian K, Harding IC, Herman IM, et al. Blood-brain barrier damage in ischemic stroke and its regulation by endothelial mechanotransduction. *Front Physiol* 2020; 11: 605398.
54) Zhu F, Anadani M, Labreuche J, et al. Impact of antiplatelet therapy during endovascular therapy for tandem occlusions: a collaborative pooled analysis. *Stroke* 2020; 51: 1522–1529.