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Neurocritical Care Updates in Cerebrovascular Disease

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Discoveries in cerebrovascular disease across the translational science spectrum emerged last year. The first single-cell atlas of the normal and malformed brain vasculature was published[1]. Mesenchymal stromal cells (MSC) were administered intranasally for perinatal ischemic stroke.[2] Thrombectomy trials exploring additional indications continued[3–5]. Precision-medicine developments in cardiac arrest and subarachnoid hemorrhage were reported, and the American Heart Association published guidelines for intracerebral hemorrhage (ICH) after 7 years. Here we summarize key highlights from four common cerebrovascular diseases in neurocritical care (NCC) units: acute ischemic stroke (AIS), ICH, cardiac arrest (CA), and subarachnoid hemorrhage (SAH).

Ischemic Stroke

Endovascular Trials

AURORA, the individual data meta-analysis of 505 patients from six late-time window endovascular therapy (EVT) randomized controlled trials (RCT) reported higher functional independence (modified Rankin Scale [mRS] score 0–2) with EVT vs medical management (MM, 45.9% vs 19.3%, p<0.0001)[4]. There was no effect on mortality or symptomatic ICH. Although earlier EVT had higher rates of favorable outcome, treatment effect appeared greater in the delayed 12–24h time-window (odds ratio [OR]=5.86) vs 6–12h (OR=1.76). The reasons remain unclear and may relate to higher alteplase proportions in the earlier group, underlying pathobiology, group imbalances (age, occlusion type), or chance. In all six individual trials there was a maximum infarct volume (<51–70 ml) or minimum ASPECTS (Alberta Stroke Program Early Computed Tomographic Score >5–6) due to concerns for reperfusion hemorrhage or extensive infarction precluding functional independence. Observational studies suggest that these concerns may be overestimated[6], nonetheless EVT access for patients with large cores remains limited.

Enter RESCUE-Japan-LIMIT[3]. In this RCT of 203 patients with ASPECTS 3–5, EVT improved the 48h NIHSS by ≥8 points and 90d mRS 0–3 (58% with EVT vs 31.4%

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with MM, p<0.001) despite an increase in any ICH. The ordinal shift favored EVT with the largest benefit in the mRS-5 group: 39.2% with MM vs 18% after EVT. However, median baseline infarct volumes were 94–110 ml, and there was no clear benefit in patients with thrombolysis or treatment >6h suggesting that the study enrolled moderately but not extremely large infarcts. Additional large-core RCTs including ANGEL-ASPECT (NCT04551664), TESLA (NCT03805308), IN EXTREMIS LASTE (NCT03811769), SELECT2 (NCT03876457) and TENSION (NCT03094715) are ongoing. These have implications for NCC clinical/post-procedural protocols and research especially hemodynamic and cerebral edema management. Future large-core studies combining EVT with other drugs/agents (e.g. Nerinetide, BIIB093/glyburide) are promising avenues given the potential synergy.

Much like the history of anterior circulation LVO, initial RCT data for basilar artery occlusion from BEST[7] and BASICS[8] suggested no benefit of EVT. However, poor recruitment and high crossover rates compounded an existing lack of equipoise. Results from two multicenter Chinese RCTs BAOCHE (NCT02737189) and ATTENTION (NCT04751708) were presented at the 2022 European Stroke Organization Conference. ATTENTION randomized 342 patients within 12h to EVT vs MM. Better 90d outcomes including mRS 0–3 (adjusted risk-ratio 2.1, p<0.001) and functional independence were observed. BAOCHE further pushed this boundary and randomized 217 patients within 6–24h to EVT vs MM. Here, 90d mRS 0–3 rates improved from 24.3% to 46.4% with a number needed to treat of 4.5. Functional benefit for both was noted despite higher rates/trends of symptomatic ICH.

Post-Stroke care

Hemodynamics: Our previous update discussed the 2019 American Heart Association (AHA)/American Stroke Association (ASA) guidelines and data for blood pressure (BP) post EVT[9]. An individual patient data meta-analysis with 5874 patients reported that higher mean systolic BPs 24h post EVT (per 10 mmHg) were associated with several unfavorable outcome measures[10]. Findings were robust regardless of recanalization or thrombolysis, however causality cannot be inferred. No nadir/U-shaped relationship was reported. This differed from BP-TARGET which reported no outcome differences between intensive (100–129 mmHg) vs standard (130–185 mmHg) BPs post EVT. However, in BP-TARGET, achieved BPs were only modestly different between groups: 128±11 vs 138±17mmHg. ENCHANTED-2 (NCT04140110, <120 vs <140–180) and OPTIMAL-BP (<180 vs <140 mmHg, NCT04205305) results are pending.

Tracheostomy: SETPOINT-2 randomized 382 patients with AIS or hemorrhagic stroke (ICH and SAH) to early (≤5d from intubation) vs. standard tracheostomy. Unlike the pilot study and retrospective data, early tracheostomy did not benefit 6-month survival without severe disability. However, the study was not powered for subgroup analyses by disease type (~30% SAH, ~30% AIS, ~40% ICH), and confidence intervals were wide precluding definitive conclusions. The data also suggested potential heterogeneous responses with age, sex, and location of center (US vs Germany). The question of whether early tracheostomy is

beneficial in acute brain injury thus remains unanswered; strategies may need to be tailored to individual clinical circumstances.

Recovery

The first safe and feasible intranasal MSC delivery was reported in human stroke[2]. Performed in 10 neonates with perinatal arterial AIS and pre-study Wallerian degeneration, the procedure was well tolerated. Although not powered to assess efficacy, 60% of patients had resolution of radiographic asymmetry by 3 months vs the natural history of 0–38%. MSC distribution/homing was not evaluated. If this strategy is validated/beneficial, it may revolutionize a minimally invasive approach for recovery and regeneration.

Intracerebral Hemorrhage

The 2022 AHA/ASA guidelines for spontaneous ICH emphasized NCC[11]. They provide practical direction for acute BP management by synthesizing the individual results and secondary analyses of two previously discussed phase-III trials (ATACH-2 and INTERACT-2). A Class-2a recommendation was provided to initiate acute BP lowering within 2h of ICH onset, with emphasis on smooth/gradual titration to improve functional outcome. The degree of BP reduction may vary with patient characteristics like ICH severity and presenting SBP- for mild-moderate ICH and presenting SBP of 150–220 mmHg, a Class-2b recommendation suggests a target of 140 mmHg, however lowering SBP<130 mmHg may be harmful (Class-3 Harm/Strong). Further studies are warranted on mode of reduction and optimal BPs for patients with SBP>220 mmHg or lobar ICH.

Vitamin-K antagonist-related ICH and international normalized ratio (INR)>2 now has a Class-1 recommendation for reversal with 4-factor prothrombin complex concentrates (PCC) in preference to fresh-frozen plasma. For direct oral anticoagulants, andexanet alpha (factor Xa inhibitor related ICH) and idarucizumab (dabigatran related ICH) have class-2a recommendations for reversal. Absent their availability, four-factor or activated PCC may be used (Class 2b). For dabigatran reversal, renal replacement therapy could be considered (Class 2b). Antiplatelet reversal includes desmopressin (Class 2b). Supported by PATCH, in the absence of emergent surgery, platelet transfusions are considered harmful (Class-3 Harm/Strong). Despite tranexamic-acid's (TXA) reduced hematoma expansion and possibly early mortality, there is no established benefit on functional outcome. Both Factor VIIa and TXA are currently considered investigational.

Cardiac Arrest

Improving outcomes after CA remains a challenge. Results from the follow-up study on ex-vivo brain cellular function post-arrest[12] are imminent. In a multicenter RCT, 501 patients with in-hospital CA were randomized to standard advanced life support (including epinephrine) with vs without vasopressin and methylprednisolone[13]. Despite increased likelihood of return of spontaneous circulation, there was no effect on survival or neurological recovery. This may partly be because glucocorticoid continuation was not stipulated post-resuscitation, and pulseless electrical activity was over-represented as the initial rhythm (54%).

Aggressive treatment of electroencephalographic (EEG) abnormalities post-CA was similarly disappointing: TELSTAR randomized 172 patients to standard care with or without complete suppression of rhythmic/periodic EEG activity for 48h[14]. Despite suppression in 56% within the treatment group (vs 2% with standard care), there was no difference in outcome or mortality. However, >60% of the patients had myoclonus which, depending on the electrographic phenotype, may have skewed the population towards unfavorable outcomes regardless of treatment. The trial will provide preliminary data regarding patterns like periodic discharges for future studies. EEG patterns are increasingly recognized as informative biomarkers. A post-hoc analysis of the Targeted Temperature Management trial revealed that neurofilament levels were 13X higher in patients with malignant vs benign EEG patterns and the extent of brain injury was more strongly related to background rather than superimposed discharges[15]. Imaging (e.g. MR-spectroscopy[16]) and serological (e.g. neuron specific enolase[17]) biomarkers for neuro-prognostication are also valuable. Ultimately a multi-modal approach will likely facilitate deep phenotyping enabling more robust neuro-prognostication and targeted treatment strategies.

SAH and brain vasculature

Clazosentan received approval for preventing vasospasm, vasospasm-related cerebral infarction, and cerebral ischemic symptoms after aneurysmal SAH by the Japanese Pharmaceuticals and Medical Devices Agency in 2022. This was supported by two Japanese multi-center phase-III RCTs in 442 patients demonstrating reduced vasospasm-related morbidity and all-cause mortality with clazosentan (10 mg/h)[18]. Given the dose-response from CONSCIOUS-1 and recent Japanese approval, despite null results in CONSCIOUS-2 (5 mg/h)[19] there may be future interest in exploring the higher-dose.

A precision-medicine retrospective analysis of 39 prospectively enrolled patients identified an increase in optimal cerebral perfusion pressure (CPP) 30h prior to delayed cerebral ischemia (DCI), followed by a discrepancy between optimal vs actual CPP ~3h before DCI thus identifying an actionable target for future research[20]. Like CA, a multimodal approach combining CPP, EEG and transcranial doppler data[21] may improve DCI detection, phenotyping and treatment.

2022 also produced a first-in human single-cell atlas detailing the transcriptomic heterogeneity of the normal and malformed brain vasculature (from arteriovenous malformations)[1]. This is a pivotal foundational step towards deconstructing disease heterogeneity, facilitating mechanistic understanding, and accelerating the development of targeted therapies for a spectrum of cerebrovascular disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

4F-PCC	4-factor prothrombin complex concentrates
AHA	American heart association
AIS	acute ischemic stroke
ASA	American stroke association
ASPECTS	Alberta Stroke Program Early Computed Tomographic Score
BP	blood pressure
CA	cardiac arrest
CPP	cerebral perfusion pressure
DCI	delayed cerebral ischemia
EEG	electroencephalographic
EVT	endovascular therapy
ICH	intracerebral hemorrhage
INR	international normalized ratio
LVO	large vessel occlusion
mRS	modified Rankin scale
MSC	mesenchymal stromal cells
NCC	neurocritical care
NICU	neurointensive care unit
OR	odds ratio
RCT	randomized controlled trial
SAH	subarachnoid hemorrhage
SBP	systolic blood pressure
TXA	tranexamic acid

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