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2023 Neurocritical Care Updates in Cerebrovascular Disease

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Research advances in cerebrovascular neurocritical care (NCC) over the past year span ischemic and hemorrhagic disease. Thrombectomy trials for large ischemic cores including an extended time-window have shown promise[1–3]. The debate on hemodynamic management after endovascular therapy (EVT) for acute ischemic stroke (AIS) persists - increasingly suggesting that generalized blood pressure (BP) reduction may be harmful. Further investigations explore a potential role for precision medicine[4–7]. Amyloid-related imaging abnormalities (ARIA) in the context of anti-amyloid immunotherapies have been brought to the forefront given the rare but potentially fatal consequences of cerebral edema and hemorrhagic transformation[8,9]. Drug approval now sets the stage for unexpected overlap between NCC and Alzheimer's disease. The American Heart Association (AHA) and Neurocritical Care Society (NCS) independently published guidelines for aneurysmal subarachnoid hemorrhage (ASAH) after >10 years[10,11]. Here, we summarize key research highlights.

Ischemic Stroke

- **Endovascular Trials**

  RESCUE-Japan-LIMIT was the first randomized controlled trial (RCT) suggesting EVT benefit in 203 patients with large ischemic cores (Alberta Stroke Program Early Computed Tomographic Score [ASPECTS] 3–5)[12]. While promising, there was no benefit beyond six hours or with ASPECTS 0–3 in a post-hoc secondary analysis (not powered by the initial study) thus raising questions about subgroups applicability[13]. ANGEL-ASPECT[3] and SELECT2[1] expanded the time-window of EVT benefit for patients with large-cores- both were halted early for efficacy.

  ANGEL-ASPECT randomized 456 patients in China (ASPECTS 3–5, or infarct 70–100 ml) within 24h of last known well (LKW) to either EVT or medical management. The second interim analysis yielded benefit in primary outcome (90-day modified Rankin scale [mRS]

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shift). Again, infarcts were moderate not large. Unlike RESCUE-Japan-LIMIT, a greater proportion (>60%) of patients were enrolled beyond 6h and benefit was observed with EVT (odds ratio [OR]=1.55, 95% confidence interval [CI]=1.17–2.0). There were higher odds of any intracranial hemorrhage (ICH) within 48h with EVT (OR=2.07, p<0.001). Symptomatic hemorrhage and decompressive craniectomy were higher with EVT although this did not meet statistical-significance. Edema and hemorrhage may thus be important in the larger core (>70 mL) subgroup. There was no mortality benefit at 90 days potentially reflecting the more moderate infarct volumes.

Similarly, SELECT2, an RCT of 352 patients across North America, Europe, Australia and New Zealand, included patients with ASPECTS 3–5 but a smaller infarct core threshold (≥50ml). Median infarct volumes were ~80 ml. Subgroup analysis demonstrated EVT benefit across age, NIH stroke scale scores, time from LKW, infarct volume (including ≥150ml), mismatch ratios. The rate of sICH was low (~1%) in both arms. Early neurologic worsening was numerically (not statistically) higher with EVT- these patients had worse 90-day outcome. Although no definitive conclusions can be drawn, these patients may warrant close NCC monitoring and management.

TESLA was presented at the 2023 European Stroke Organization Conference (ESOC) as a pragmatic-approach trial[14] that used CT-based infarct volumes (vs advanced imaging) for patient selection, and expanded the inclusion threshold to ASPECTS 2–5. TESLA narrowly missed its primary endpoint however there were no safety concerns. A recently published meta-analysis of all four large core trials demonstrated that while sICH was greater with EVT, clinical/outcome benefit persisted[2].

Currently, the large-core trials affirm that patients with moderate-large-core (~50–100cc) likely benefit from EVT. There remain unanswered questions about differences in hemorrhage rates between the studies, and etiology of early neurological deterioration without hemorrhagic transformation (SELECT-2). The lack of mortality benefit may reflect the moderate-large vs truly large-core infarct volumes tested. Questions of ‘is there an infarct size that is ‘too big to treat’ with EVT?,’ or ‘is non-contrast CT sufficient to triage patients?’ remain. Results from both TESLA and LASTE (NCT03811769)[15] will be informative and potentially revolutionize the EVT landscape once again- although there remains debate about this.

- **Hemodynamic Management After EVT**

The relationship between BP and AIS, particularly after EVT, remains complex. An individual patient data analysis from seven RCTs demonstrated a non-linear association between admission systolic BP (SBP) and functional outcome, with an inflection point at 140 mmHg[4]. Patients with ≥140 mmHg were associated with unfavorable outcome. There was no interaction with EVT; the authors note that elevated SBP should not dictate thrombectomy treatment decisions.

Previously we discussed an individual patient data meta-analysis where higher mean SBPs post EVT were associated with unfavorable outcomes[16,17]. ENCHANTED-2/MT (a multicenter open-label blinded RCT) is now completed with 821 patients randomized to

more (<120 mmHg) vs less intensive (140–180 mmHg) SBP control for 72h[5]. Again, odds of worse primary outcome (ordinal mRS analysis) were greater with intensive treatment (OR=1.37, 95% CI 1.07–1.76). Most patients achieved their target SBPs and TICI-3 recanalization (83–84%)- thus, even with open large vessels the risk of compromising the cerebral microcirculation may outweigh concerns of reperfusion injury. Caution against generalized BP reduction post-EVT and support for an individualized approach was supported by OPTIMAL-BP and BEST-II presented at the 2023 ESOC and International Stroke Conference. CRISIS-1 (NCT04775147, SBP <120 vs 140 mmHg) and HOPE (NCT04892511, standard of care vs SBP 140–160mmHg if TICI-2b vs SBP <140 mmHg if TICI-2c/3) will be informative, particularly with the latter accounting for the potential importance of recanalization extent in subsequent hemodynamic requirements.

ICH

- **Surgical clot evacuation**

  ENRICH is the first surgical trial to suggest functional benefit of minimally invasive clot removal in ICH[18]. Presented at the 2023 American Association of Neurological Surgeons conference, it is a Bayesian adaptive comparative-effectiveness study that randomized patients with anterior basal ganglia (ABG, n=92) or lobar (n=208) ICH to minimally invasive trans-sulcal parafascicular surgery (MIPS) ± guideline based medical management within 24h of LKN. The study enriched for lobar-ICH when the stopping criterion for ABG ICH was met. The primary outcome (utility-weighted mRS) at 6-months demonstrated treatment benefit. Results (pending publication) suggest a promising therapy for improving patient-outcomes at least in supratentorial lobar ICH.

- **NCC Hemodynamic Management and Prognostication after ICH**

  INTERACT-3 (international multicenter blinded RCT) in 7036 patients from predominantly low- and middle-income countries demonstrated benefit of a goal-directed care bundle that incorporated protocols for BP lowering, hyperglycemia, pyrexia and anticoagulation[19]. Most patients (~82%) had deep ICH. The reduced odds of unfavorable functional outcome (OR=0.86, 95% CI 0.76–0.97) was consistent across multiple sensitivity analyses.

  Notwithstanding the benefit of goal-directed care bundles, death and disability was high in INTERACT-3 despite a high median presenting Glasgow Coma Scale score (GCS=9). Neuro-prognostication after ICH remains challenging and will evolve as treatments advance. A post-hoc analysis of pooled individual data in severe ICH and IVH survivors (from CLEAR-III and MISTIE-III) evaluated 1-year recovery trajectories and determined that ~43% of patients with initially poor outcomes (30-day mRS 4–5) recovered to good outcome by 1 year (mRS 0–3)[20]. By 1 year, 64.6% of these patients had returned home. Including granular data like pre-existing conditions, hospital events, and response to therapy improved model discrimination (and identifies targets to improve long term recovery). The study reminds us to side-step self-fulfilling prophecies and allow for longer evaluation periods and nuanced discussions prior to neuro-prognostication.

- **Antiseizure Medications after ICH**

  The jury remains out on seizure prophylaxis after ICH. PEACH randomized 50 patients to 500 mg levetiracetam every 12h vs placebo for six weeks[21]. Only 48% of the recruitment target was reached and the data were not powered for efficacy. Three of 19 patients in the levetiracetam group (16%) had electrographic seizures versus ten of 23 in placebo (43%, OR 0.16, p=0.043). Most patients had deep ICH, small hematoma volumes, and were predominantly mild (median GCS=15, interquartile-range=14–15) potentially decreasing the generalizability. The impact on clinical seizures and outcomes remains to be determined in future work with larger trials.

- **ARIA**

  An unexpected overlap between Alzheimer's disease and cerebrovascular NCC has emerged with the approval of several anti-amyloid immunotherapies associated with ARIA. Although ARIA-edema/effusion (ARIA-E) and ARIA-hemorrhage (ARIA-H) have been reported in 6.5–80%, the incidence/risk varies. There is higher risk with specific immunotherapies, dose-dependence, APOE-ε4 haplotype, anticoagulation use, and baseline characteristics (preexisting cerebral amyloid angiopathy). Most cases remain mildly/ asymptomatic, however there have been rare reports of severe and fatal brain swelling and hemorrhage[8,9,22–27]. For treatment, cessation of immunotherapy has been combined with high-dose corticosteroids, serial imaging, and anticonvulsants if needed[23,25]. ARIA's putative pathophysiology involves mobilization of Aβ deposits in the vasculature when they are bound by anti-Aβ antibodies, thus disrupting vascular integrity[24]. ARIA-E and ARIA-H frequently co-occur, suggesting mechanistic overlap- this continuum has been proposed previously as it relates to the sulfonylurea-receptor-1—transient receptor potential cation subfamily-M member-4 channel[28,29]. Understanding the relationship between Aβ plaques, APOE-ε4, and other channels implicated in cerebral edema may guide development of targeted molecular therapy across several diseases in NCC.

ASAH

- **Guidelines**

  2023 NCS and AHA guidelines for ASAH presented several updates after an ~10 year hiatus[10,11]. Here we highlight some differences between guidelines book-ending the past decade. NCS guidelines no longer target a specific BP prior to aneurysm treatment. Both societies recommend against statins, endothelin receptor antagonists and antifibrinolytic therapy. NCS guidelines noted insufficient data to recommend for-or-against BP and cardiac output augmentation (including milrinone), triggers for interventional procedures, mineralocorticoid therapy, or a transfusion threshold > 7g/dL. AHA guidelines that present similar data and delineate the lower class of recommendation and level of evidence while suggesting it is reasonable to augment SBP, cardiac output, and intra-arterial vasodilator therapy. AHA noted harm with phenytoin for seizure prevention/ prophylaxis and the lack of benefit of antiseizure medications beyond 7-days in patients with seizures but without prior epilepsy. AHA guidelines emphasized the importance of healthcare systems/access, critical-care bundles, trained nurses and multidisciplinary teams. Core treatments like oral nimodipine and avoidance of hypervolemia were unaltered.

- **Cerebrospinal Fluid (CSF) Drainage**

  EARLYDRAIN randomized 307 patients from 19 centers to 'standard care' versus an additional lumbar drain (LD) after ASAH[30]. There was a reduced risk ratio (RR) of unfavorable outcome in the LD group (RR=0.73, 95% CI 0.52–0.98) and fewer secondary infarctions at discharge (RR=0.71, 95%CI 0.49–0.99). It is challenging to extrapolate these data to current practice where patients receive either LD or EVD but rarely both- in EARLYDRAIN, 70.8% of patients in the LD group and 76.9% of patients in the standard group also had external ventricular drains (EVD). Although adjusted for statistically, a greater proportion of patients in the LD group had a lower ASAH grade. Despite some of these challenges, there was marked color difference in EVD vs LD CSF when used simultaneously- supporting the hypothesis of erythrocyte sedimentation by weight and potentially easier removal by LD. It was reassuring, that only one patient developed an increasing gradient of >5 mmHg in intracranial pressure from EVD vs LD. While this RCT does not answer the question of whether LD alone is superior to EVD after ASAH (since majority of patients in the LD group received both), it appeared safe in conjunction with EVDs. An adequately powered RCT of LD in ASAH is needed. Importantly, these data are hypothesis-generating regarding potential mechanisms of reduced cerebral ischemia and improved outcome in ASAH.

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Abbreviations:

AHA	American heart association
AIS	acute ischemic stroke
ARIA	Amyloid-related imaging abnormalities
ASPECTS	Alberta Stroke Program Early Computed Tomographic Score
BP	blood pressure
CI	confidence interval
EVT	endovascular therapy
ICH	intracerebral hemorrhage; LVO=large vessel occlusion
mRS	modified Rankin scale
NCC	neurocritical care
OR	odds ratio

RCT	randomized controlled trial
RR	Risk Ratio
SAH	subarachnoid hemorrhage
SBP	systolic blood pressure

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