Optimization of Neurological and Functional Recovery Following Cardiac Arrest

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Sudden cardiac arrest (SCA) remains one of the major challenges in clinical care. Although improvements in resuscitation quality have increased the likelihood of return of spontaneous circulation (ROSC), most patients still fail to survive to hospital discharge, and neurological injury is the leading determinant of poor outcome. Hypoxic-ischemic encephalopathy caused by global cerebral hypoxia during cardiac arrest is a key contributor to long-term disability, and even survivors often experience substantial functional impairment, placing a significant burden on families and society. Targeted temperature management (TTM) has long been regarded as a cornerstone neuroprotective strategy; however, TTM and TTM2 trials reported no significant neurological difference between lower and higher temperature targets. However, these studies predominantly enrolled patients with relatively mild illness severity, and multiple real-world observational cohorts suggest that, among more severely ill resuscitated patients, lower target temperatures may still confer benefit. Consequently, the optimal temperature strategy in higher-risk subgroups remains uncertain.

Seizures are another common manifestation of brain injury after cardiac arrest, occurring in approximately 20–30% of resuscitated patients and contributing to secondary neurological damage. Earlier trials evaluating prophylactic anti-seizure medication (ASM) (thiopental or diazepam/magnesium) did not demonstrate neurological benefit; however, these studies primarily focused on neuroprotection rather than seizure prevention, leaving a substantial evidence gap. Patients with moderate to severe disease severity—those at the highest risk of both cerebral injury and seizure occurrence—have never been specifically studied to determine whether personalized temperature selection or early short-term prophylactic ASM (e.g., valproic acid or levetiracetam) may provide clinical benefit.

Accordingly, identifying the most appropriate temperature target for higher-risk patients and determining whether short-term prophylactic antiepileptic therapy can reduce seizure-related injury represent important unresolved questions in post-resuscitation care. The aim of this study is to conduct a prospective, multicenter, randomized clinical trial to evaluate whether, among comatose

patients with moderate to severe risk after ROSC, specific TTM temperature strategies combined with early short-term prophylactic ASM can reduce postresuscitation seizure incidence and improve neurological outcomes.

By addressing a population underrepresented in prior clinical trials—those at highest risk and most likely to benefit—this study aims to generate clinically meaningful evidence to guide temperature selection and prophylactic ASM after cardiac arrest. Evaluating these interventions in combination may provide a more comprehensive understanding of whether they reduce seizure burden, mitigate brain injury, and improve functional recovery.