Early case fatality in intracerebral hemorrhage
Sophistication of care, application globally

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Acute spontaneous (nontraumatic) intracerebral hemorrhage (ICH), presumed due to cerebral small vessel disease, remains a serious and difficult-to-treat form of stroke. The 1-month case fatality of ICH is around 40%, with half of the deaths occurring in the first few days after onset. This outlook has remained largely unchanged during the last decades. The consistently high case fatality, in combination with the diverse etiologies of ICH, may have hampered development of acute evidence-based management strategies. Similarly, despite improved management of vascular risk factors including hypertension, the overall ICH incidence is stable, possibly due to the aging of the population and the more widespread use of antithrombotic drugs, such as for atrial fibrillation. To consolidate epidemiologic knowledge about early case-fatality trends of ICH in the last decades and identify clinical needs in the acute setting, well-designed prospective population-based studies are needed.

In this issue of Neurology®, Béjot et al. report important new data on the topic by utilizing the Dijon Stroke Registry. This is a powerful population-based registry that prospectively and continuously collected all first-ever spontaneous ICH cases among the well-characterized inhabitants of Dijon, France (n = 152,000), from 1985 to 2011. The article assessed the temporal trends in both very early (within 48 hours) case-fatality rates and those occurring between 48 hours and 30 days in ICH patients, a unique approach compared to previous studies. These outcomes were compared using appropriate multivariable models across 3 periods: 1985–1993, 1994–2002, and 2003–2011. The authors report that between these time periods, there has been no change in case-fatality rates within the first 48 hours, while a decrease in case-fatality rates occurred between 48 hours and 30 days in adjusted models.

The findings support the study’s original hypothesis. Better management of ICH patients, especially organized intensive care unit and stroke unit treatment or prevention of post-ICH complications, could underlie the reduced deaths between 48 hours and 30 days. Nevertheless, these data also suggest that no strategy has improved very early mortality over the last 3 decades: the early case fatality accounted for an increasing proportion of deaths (38%–51%). The authors postulate a missed opportunity, that advances in acute management are needed to address very early case fatality (within 48 hours) in ICH patients. Indeed, evidence-based recommendations for acute ICH management are largely based on empirical guidelines due to absence of successful large randomized controlled trials, representing a major unmet need in the field. An alternative possibility is that early ICH care may already be optimized and very severely affected patients inevitably face high early mortality. In this context, clinical nihilism could prevail, with patients’ families and doctors deciding that the ICH is too severe to allow recovery to a meaningful quality of life, and thus aggressive lifesaving measures, not perceived to alter this predicted poor outcome, are not appropriate. This scenario may be common, since the authors mention that surgery was rarely pursued in their study. An added complicating factor is that it is often difficult to reliably predict ICH patient outcome at the time of initial presentation. Premature use of do not resuscitate or withdrawal of care orders is an independent predictor of mortality.

These new data highlight an overall improvement in ICH case fatality over time, with the benefit largely obtained in the post-48-hour period, but not in very early case fatality. In the very acute ICH setting, the only recommended emergency medical therapeutic option is early aggressive control of elevated blood pressure (>140 mm Hg), endorsed by the American Heart Association/American Stroke Association in 2015 and the European Stroke Organisation in 2014. These updated recommendations were largely based on the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT2). The more recent results of the second Antihypertensive Treatment for Acute Cerebral Hemorrhage (ATACH -II) study may lower initial enthusiasm for aggressive blood pressure lowering in ICH, but there are key differences between the 2 trials. Of note, the registry observation period by Béjot and colleagues ended in

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2011, i.e., before the INTERACT2 results and the implementation of updated guidelines of acute blood pressure lowering in ICH. Ongoing data from an extended time period within the Dijon Stroke Registry or other prospective population-based registries will be valuable to further unravel trends in mortality after the implementation of intensive blood pressure-lowering strategies.

Key variables not available in the current study registry might have been relevant for the interpretation of the results. First, the proportion of very early deaths that occurred in patients who came in moribund condition (e.g., massive ICH in deep coma) were not available; comparison would be valuable to those who deteriorated after hospital arrival (but still within 48 hours). Moreover, there was no ICH or NIH Stroke Scale score on admission, hence ICH severity; this was only partially adjusted for by considering proxies of severity, including decreased level of consciousness and motor impairment. Though prevalence of decreased level of consciousness was lower across the study timeframe, the inclusion of this proxy to fully adjusted models did not change the effect sizes. Second, it would have been interesting to explore changes in hospital arrival time for ICH—if the health system delivers these patients to the hospital faster, there could be a better chance for effective interventions. Finally, knowing something about the mechanism of these ICH deaths may have furthered our understanding of why there were no changes over time in very early deaths. Were most of the very early deaths the result of limitations of life support or brain death, as suggested in some studies?10,11 Was the later reduction in mortality related to reduced complications from better stroke unit or ICU care? Did these proportions change over time?

Thinking more broadly, the global burden of ICH is huge, with the majority of cases occurring in low- and middle-income countries.12 Although these results compel efforts to discover more effective very early interventions for ICH, the improved post 48 hours mortality suggests a global opportunity to replicate the conditions in Dijon, where they are not currently available. Identifying these factors with efforts to implement more broadly could effect a major reduction in global ICH mortality. Since acute ICH is a complex and etiologically diverse condition, larger studies, in diverse care settings, with adequate power to dissect ICH case-fatality trends within specific patient subgroups, e.g., in older patients, antithrombotic-related ICH, per hematoma expansion, and other acute markers, will be valuable.

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