JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 65, NO. 19, 2015

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jacc.2015.03.554

EDITORIAL COMMENT

Between Death and Hope After Out-of-Hospital Cardiac Arrest

Should We Rely on Biomarkers?*

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"Lasciate ogni speranza di riveder lo cielo o voi che entrate."
—Dante Alighieri's *Divina Commedia* (1)

These words, on the entrance of the "Inferno" in the *Divina Commedia*, translate as "Abandon all hope you who enter here." Fortunately, these words are inappropriate in contemporary medicine: mortality is getting lower in all areas, and even those who experience a resuscitated, out-of-hospital cardiac arrest (OHCA) have good "hopes" of leaving the hospital alive, with few or no neurological reliquats (2). However, in many life-threatening conditions, including OHCA, physicians still lack information on the likelihood of a patient's recovery. The experience of an OHCA is dramatic for patients' relatives and often frustrating for doctors. Both may feel helpless, as the risk of death and no cerebral recovery is still high. A recent collaborative study in Northern Europe (3) found a survival rate in OHCA around 50%. Although the good news was that only 10% of those who survived had severe neurological impairment, this study further raises interest in any tool that might improve prognosis or prognostication of recovery. Prognostication on the fate of these patients is, indeed, difficult, and our ability to predict their outcomes often includes guesswork. In the past, the majority of studies used the Glasgow Outcome Scale and the Cerebral Performance Category to assess prognosis after OHCA; both methods are based on neurological examinations and, therefore, are intrinsically limited by the post-cardiac arrest conditions, including sedation (3). Conversely, management of OHCA patients would require effective prognostic methods to correctly allocate resources and reduce some stress for the patient's relatives. This issue obviously raises important ethical considerations.

SEE PAGE 2104

In this issue of the *Journal*, Stammet et al. (4) report on the possibility that neuron-specific enolase (NSE) might improve prognostication in OHCA in addition to the current clinical and biological indexes. NSE is a dimeric intracellular glycolytic enzyme comprised of 2 subunits, $\gamma\gamma$ or $\alpha\gamma$, present in neurons and in other cells of neuroectodermal origin, but they also are found in erythrocytes (5) and platelets (6). Serum NSE has been widely used in OHCA and is the only biochemical marker of brain injury accepted for neurological prognostication after cardiac arrest (7,8). Recent studies on hypothermia after cardiac arrest, however, gave conflicting results, questioning the relevance of recommended cut-off values and reducing the interest in this biomarker (9,10). Methodological issues surfaced, questioning the robustness of the analysis in conditions such as hemolysis (11,12), whereas the small number of patients enrolled in previous studies might explain, under a statistical point of view, the variability of the results (7).

What does the study by Stammet et al. (4) add to all this? Taking advantage of the robustness of the TTM (Target Temperature Management After Cardiac Arrest) trial (13), which demonstrated the lack of

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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advantage of brain cooling at 33°C versus 36°C after OHCA, they had the possibility to approach the issue of NSE as a prognosticator of survival in these patients. TTM, a multicenter, randomized trial, enrolled 939 patients, of whom 686 had complete data and blood samples at 3 different times (24, 48, and 72 h after return of circulation). Neurological prognostication and withdrawal of life-supporting therapies were standardized according to the TTM trial protocol. The primary outcome of the study was neurological function at 6 months, dichotomized to good or poor outcome according to the Cerebral Performance Category scale. Secondary outcomes were good or poor, according to the modified Rankin scale at 6 months and all-cause mortality at the end of the trial. NSE was found to be a robust predictor of outcome. There was no significant difference between temperature groups at any time point for any of the study's outcomes.

As a major strength, this investigation was a predefined substudy investigating a serum biomarker for prognostication after OHCA within the largest, multicenter, randomized clinical trial studying 2 target temperature regimens in comatose cardiac arrest patients. It represents the largest prospective study of its kind. Other studies reporting lower NSE values in 33°C-treated patients had limitations, notably due to the comparison of patients treated at 33°C to historical control subjects (14) or to a small sample size (15). The results of NSE values were not available to the treating physicians during the trial and, therefore, did not influence prognostication of patients. A unique feature of the TTM trial is that prognostication and withdrawal were standardized, which increases the validity of the results on NSE of the current study (13).

Moreover, the study methodology is strong and convincing. All analyses were performed in a single core laboratory limiting the influence of assay variability and laboratory processing; samples with hemolysis were eliminated from the study. The statistical analysis was reliable. NSE levels at 24, 48, and 72 h were added to a clinical multivariable logistic model containing temperature allocation, age, sex, bystander cardiopulmonary resuscitation, first monitored rhythm, time from cardiac arrest to return of spontaneous circulation, lactate levels, and circulatory shock on admission.

Thus, the study convincingly demonstrates that adding NSE to the other clinical parameters significantly improves the ability to predict a poor neurological outcome. High NSE cut-off values (with ≤5% false positive rates and tight 95% confidence intervals) at 48 and 72 h offer reliable prediction of poor outcomes with sufficient sensitivity to remain clinically useful within a multimodal prognostication package, including clinical examination, imaging, neurophysiology, and biomarkers.

However, the authors themselves point out some limitations of their study. Although a pre-defined substudy of the TTM trial, not all sites enrolling in the main trial participated in biomarker sampling. Not all patients had blood samples taken at every time point, and there was no external quality control at each participating site where samples were collected and pre-analytically processed.

Second, although biomarkers are unaltered by sedation and may, therefore, be a more objective marker of brain injury, they have a general limitation that their measurement is punctual, whereas production or secretion is a dynamic process, highlighting the importance of serial measurements to best predict outcome. Furthermore, brain biomarkers measured in circulating blood might have some additional weaknesses, as the integrity of the blood-brain barrier after ischemia-reperfusion injury in individuals cannot be measured and may vary substantially. In the case of NSE, which is predominantly released from neural and neuroendocrine cells, caution is warranted as serum levels might reflect variable degrees of brain damage.

A further limitation may be the scarcity of cardiological data that might affect recovery, such as blood pressure or left ventricular ejection fraction. Nevertheless, these data will provide a milestone for the next years in studies on OHCA and a reference for clinicians dealing with this issue.

These study results also indicate additional considerations. The evidence of a significantly better neurological outcome in OHCA for those who were resuscitated by a bystander suggests that efforts to improve the knowledge of basic life support in the general population and the availability of automatic defibrillators in the proper locations are integral. Also, the availability of different assays for NSE having different cut-off values may indeed represent a limitation for the widespread clinical use of this biomarker. Even if each assay has reliable analytical properties, comparisons are difficult, and the variability of the data generates confusion and frustration, with impossibility to apply a single decision limit to all subjects. This is similar to what is happening for troponins in cardiology, with continuous redefinition of the proper decision limits (16), and the restless search for novel biomarkers (17). However, biomarkers, often seen as the "holy grail" of medicine, must be accepted for what they are and what they can give. Few of them are near-perfect

markers of disease, none can completely separate the healthy from the unhealthy, and in many cases (as in the case of high-sensitivity troponin), biomarkers require a high level of clinical judgment from the physicians (18) for their correct utilization.

In terms of ethical, clinical questions, such as making the decision for a patient with irreversible brain death or poor neurological recovery, uncertain biomarker data should not be taken into consideration. The authors correctly propose that life support should not be ended on the basis of a biomarker level. Therefore, they recommend using NSE in a dynamic approach with serial measurements within a comprehensive prognostication protocol that includes clinical examination, electroencephalogram, brain imaging, and somatosensory (19). Once irreversible brain damage is diagnosed, it opens important bioethical issues on the continuation of care and life support. For these reasons, the need for correct prognostication in OHCA in particular, but in all fields of medicine, is important. Because we want to save the lives of our patients, provide trusted information to their relatives, and correctly allocate resources, we need a robust evidence, unfaultable methodologies, and infallible biomarkers. Therefore, studies, such as this one by Stammet et al. (4), that can improve our ability to define a correct diagnosis are welcome.

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KEY WORDS biomarker, cerebral performance, neuroprognostication, prognosis