



# The Influence of Therapeutics on Prognostication After Cardiac Arrest

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## Abstract

*Purpose of review* The goal of this review is to highlight the influence of therapeutic maneuvers on neuro-prognostication measures administered to comatose survivors of cardiac arrest. We focus on the effect of sedation regimens in the setting of targeted temperature management (TTM), one of the principle interventions known to improve neurological recovery after cardiac arrest. Further, we discuss the critical need for novel markers, as well as refinement of existing markers, among patients receiving extracorporeal membrane oxygenation (ECMO) in the setting of failed conventional resuscitation,

known as extracorporeal cardiopulmonary resuscitation (ECPR).

*Recent findings* Automated pupillometry may have some advantage over standard pupillary examination for prognostication following TTM, sedation, or the use of ECMO after cardiac arrest. New serum biomarkers such as Neurofilament light chain have shown good predictive abilities and need further validation in these populations. There is a high-level uncertainty in brain death declaration protocols particularly related to apnea testing and appropriate ancillary tests in patients receiving ECMO.

*Summary* Both sedation and TTM alone and in combination have been shown to affect prognostic markers to varying degrees. The optimal approach to analog-sedation is unknown, and requires further study. Moreover, validation of known prognostic markers, as well as brain death declaration processes in patients receiving ECMO is warranted. Data on the effects of TTM, sedation, and ECMO on biomarkers (e.g., neuron-specific enolase) and electrophysiology measures (e.g., somatosensory-evoked potentials) is sparse. The best approach may be one customized to the individual patient, a precision-medicine approach.

## Introduction

With the advent of targeted temperature management (TTM) and extracorporeal membrane oxygenation (ECMO), we entered a new era of therapeutics that fundamentally altered our ability to prognosticate and brought the well-accepted pre-TTM era guidelines into question. Further, it has become a common practice to prescribe analgesics and sedatives for at least the initial 24 h of TTM for the prevention and treatment of shivering and the duration of ECMO administration for safety and comfort. The effect of TTM, ECMO, and these pharmacologic agents on the prognostic accuracy of predictors of neurologic recovery has not been systematically evaluated. The 2006 American Academy of Neurology (AAN) guideline for outcome prediction in comatose survivors of cardiac arrest was published prior to the TTM era and recommended outcome prediction within 72 h of cardiopulmonary resuscitation and return of

spontaneous circulation [1]. In 2014, the European Resuscitation Council's advisory statement on outcome prediction recommended delaying neuroprognostication beyond 72 h if residual effects of sedation or paralysis are suspected [2].

It is especially important to understand the accuracy of prognostic testing in patients receiving ECMO during cardiac arrest or for post-cardiac arrest cardiogenic shock, as recent research shows that profound and irreversible neurological deficits are often the primary reason that surrogate decision-makers cite for withdrawal of ECMO support from a critically ill patient [3], and neurological etiologies are among the most common cause of death in ECMO patients [4]. Limited data exists regarding the extent to which ECMO may affect the prognosticators of patient recovery from acute brain injury.

## The impact of medical management on prognostication

### Indications and implications of TTM

The 2015 American Heart Association (AHA) guideline recommends that comatose adult survivors of cardiac arrest undergo TTM between 32 °C and 36 °C (class I, level of evidence (LOE) B-R for shockable rhythms with out-of-hospital

cardiac arrest; class I, LOE C-EO for non-shockable rhythms and in-hospital cardiac arrest) [5••]. The AHA suggests that TTM be maintained for at least 24 h after achieving target temperature (class IIa, LOE C-EO), but recommends against the routine prehospital cooling of patients with rapid infusion of cold fluids (class III, LOE A). Finally, the same AHA guideline states that it may be reasonable to actively prevent fever in comatose patients following TTM (class IIb, LOE C-LD) [5••]. TTM can be achieved using intravascular or surface cooling with limited data demonstrating no clear superiority of one method over another [6–8]. Shivering is the most common complication of TTM and most prominent during the induction phase when target temp is 32–34 °C and occurs regardless of target temperature chosen [9, 10]. Shivering attenuates the benefits of TTM by increasing metabolism and lowering brain oxygenation [11, 12]. Vigilant monitoring for shivering with aggressive treatment is indicated [13].

Understanding the pharmacokinetics and pharmacodynamics of sedatives and analgesics as well as the different factors that may lead to their accumulation and prolonged elimination plays a key role in prognostication in the setting of TTM. Predictors of late awakening in comatose cardiac arrest survivors treated with therapeutic hypothermia and sedation have been evaluated in a single-center observational cohort [14•]. While the use of midazolam alone [14•] or in combination with fentanyl [15•] has been shown to be associated with late awakening compared with propofol. This could be explained by the differences between midazolam and propofol pharmacokinetic properties (*see supplementary Table 1*). Physiologic alterations impacting pharmacokinetics have also been described during TTM. These include a decrease in the cytochrome P450 activity, reduction in both hepatic transformation and renal excretion, due to a decrease in hepatic and renal blood flow, respectively [16, 17]. An excess of serum drug concentrations used for sedation and neuromuscular blockade, a decrease in total body clearance, and persistence of elevated drug levels even hours after rewarming have been demonstrated in brain-injured patients receiving TTM to 32–34 °C [18–20].

## Neurological exam

In patients who receive TTM, the AHA guideline recommends [5••] waiting for 72 h after return to normothermia (class IIb, LOE C-EO) to help reduce the confounding risk of sedation and neuromuscular blockade, especially in the context of decreased drug clearance in the setting of TTM, liver injury, or acute kidney injury [21]. TTM either prolongs the time to awakening or allows those who otherwise would not regained consciousness to do so in a delayed fashion [22–27]. A post hoc analysis of the TTM trial evaluated the time until awakening after cardiac arrest and its association with the goal temperature of 33 versus 36 °C [28]. Despite receiving comparable cumulative doses of sedatives in both groups, and no difference in ultimate neurological outcome, daily awakening was delayed in patients in the 33 °C group. This might be due to decreased clearance of sedatives and analgesics at lower body temperature. In this trial, the false positive rate (FPR) of

absent pupillary reflex was 2.1% (95% confidence intervals (CI) 0.3–11.2%), and the FPR of absent corneal reflex was 2.2% (95% CI 0.3–11.4%). Though not statistically significant, both false positives were in patients cooled to 33 °C as opposed to 36 °C, which raises the issue of patients cooled to 33 °C requiring more time prior to prognostication than those cooled to 36 °C [29].

The European Resuscitation Council reported an FPR of absent pupillary reflex of 8% (95% CI 1–25%) within the first day with an improvement of 0% at 72 h both in patients treated with TTM and those not treated with TTM [30]. The AHA guideline likewise suggests that absence of pupillary reflex in patients 72 h post-cardiac arrest was a reasonable basis for poor outcome prediction with a FPR of 1% (95% CI 0–3%) in patients who have undergone TTM (class I, LOE B-NR) [5••]. However, in a subsequent study of patients receiving TTM, 5 of 78 patients (FPR 6%) with absent pupillary light reflexes on day 3 had a favorable outcome [31••].

Overall, absence of the corneal reflex seems less specific for poor outcome than absence of the pupillary light reflex. In patients treated with TTM to 33 °C, absent corneal reflex at 72–120 h predicts poor outcome with a FPR of 2% (95% CI 0–7%) [32, 33]. The FPR for absence of either pupillary or corneal reflexes at 72 h has been reported as 4% (95% CI 1–15%) at 33 °C [34] with similar findings at 36 °C [35].

Recently, investigators have assessed automated pupillometry as an advance over standard pupillary examination for prognostication following cardiac arrest. Suys et al. reported that under conditions of TTM to 33 °C with concomitant sedation, quantitative pupillometry light response is lower than in normothermic conditions in the absence of sedation [36]. Nonetheless, quantitative pupillometry has shown promise as a prognostic tool during TTM with sedation with a quoted FPR of 0% for quantitative pupillary light reactivity measure (expressed as the % of pupillary response to a calibrated light stimulus) of <7% in one and <13% in two other studies [36–38]. The Neurological Pupil index (NPi) may be an even more accurate prognosticator than the quantitative pupillary light reflex during the first days of TTM, as it may be more sensitive and less influenced by opioids and ambient light [31••].

The AHA guideline recommends that motor responses alone should not be used for predicting a poor neurologic outcome (class III harm, LOE B-NR) [5••] due to high FPRs (10–20%) associated with it of 10% (95% CI 7–15%) [33, 34].

While the brainstem reflexes are seen to be more present upon discontinuation of sedation [39], a retrospective evaluation demonstrated that while sedation decreases the positive predictive value of the absence of corneal reflexes and poor motor exam, it does not affect the prognostic accuracy of the absence of pupillary responses [40].

While any myoclonus within 72 h predicts a poor outcome (5% FPR; 95% CI 3–8%) [33, 34, 41, 42], patients with myoclonus associated with epileptiform activity on electroencephalography (EEG) seem to have a worse prognosis than those without epileptiform activity [43]. Given the high FPRs, the AHA recommends that the presence of any myoclonus should not be used to predict poor neurological outcome (class III: harm, LOE B-NR). They do suggest, however, that the presence

of status myoclonus may be used during the first 72 to 120 h after cardiac arrest in combination with other tests to predict poor outcome (class IIa, LOE B-NR) [5••]. In the TTM era, there has been a push towards increasingly sophisticated classifications of myoclonus, including consideration of the anatomical distribution, type, duration, associated EEG findings, and response to treatment [43, 44••, 45, 46, 47••].

## Electrophysiology (EEG and SSEP)

### Electroencephalography

EEG background is widely used for early prognostication and risk stratification, with several patterns correlating with poor outcome after CA. These patterns include malignant features [48, 49] such as burst-suppression pattern [50], low voltage [51, 52], status epilepticus [53–55], stimulus-induced rhythmic, and periodic or ictal discharges [56]. Conversely, presence of continuous background during the post-resuscitation phase, including the time from arrest to the development of such background is associated with good outcome [52, 57]. However, sedation is known to affect the EEG background in healthy individuals [58], and the influence of sedation on these patterns is not routinely reported. A single-center study showed that suppression ratio and amplitude-integrated EEG have been changed significantly after sedation lightening in cardiac arrest patients, with the degree of change correlating with outcome [59]. Given these factors, clinicians who attempt interpretation without taking sedation into account may make inappropriate conclusions. Another EEG-based feature, reactivity to external stimulus, has also been associated with outcome and has been reported in several evaluations of multimodal prognostication [2, 52, 60]. The effect of sedation on EEG reactivity has not been reported, although it is likely there would be changes similar to those seen with EEG background. This has resulted in the most recent international consensus for EEG reactivity reporting recommending that information on analgesics and sedatives be reported when testing EEG reactivity in cardiac arrest patients [61]. A recent study showed that a routinely used sedative, propofol, induces changes in the post-anoxic EEG, but does not affect its value for the prediction of outcome [62•].

### Somatosensory-evoked potentials

In patients who have undergone TTM, absent N20 responses after rewarming may be slightly more accurate than during TTM in prediction of a poor outcome (FPR 1%, 95% CI 0–3% vs. FPR 2%, 95% CI 0–4%) [32–34, 42, 63, 64]. The AHA reports that it is reasonable to consider bilaterally absent N20 responses 24 to 72 h after cardiac arrest, regardless of TTM, as a predictor of poor outcome (class IIa, LOE B-NR). A caveat to that recommendation is that artifact frequently limits the interpretability of somatosensory-evoked potentials (SSEPs), even in paralyzed patients [65]. Analgesics and sedatives could increase the latency and decrease the amplitude of the SSEP response in a dose-dependent

manner [21]. Despite evaluations reporting low FPR of 0.7% (95% CI 0–5%) for bilateral absent N20, when adjusted for early withdrawal of life supporting therapy, the FPR increased to 7.7% [66•]. Nonetheless, some researchers have suggested a more nuanced analysis of N20 amplitudes beyond the dichotomous presence versus absence distinction to increase the sensitivity of SSEPs to predict poor outcome [67, 68].

## Serum biomarkers

### Neuron-specific enolase and serum S-100 $\beta$ protein

Serum neuron-specific enolase (NSE), a marker of neuronal injury, is the best-studied serum biomarker for prognostication following cardiac arrest. By attenuating secondary neuronal injury, TTM may lower serum NSE levels [69]. Serum S-100  $\beta$  protein, a marker of glial injury as opposed to neuronal injury, may be less affected by TTM than serum NSE [69]. The depth and duration of TTM do not seem to have a significant effect on NSE or S-100  $\beta$  protein levels [70–72]. It is uncertain if any definite threshold exists to predict poor outcome in patients treated with TTM, but certainly, a serum NSE threshold of 33  $\mu\text{g/L}$  results in unacceptably high FPRs [32, 33, 70]. In one study, a cut-off of 151  $\mu\text{g/L}$  was needed to obtain an FPR of 0% [73]. Some of the difficulty in establishing an acceptable threshold for biomarkers like NSE or Serum S-100  $\beta$  protein may be attributable to sample hemolysis, variance in storage practices and diagnostic assays, or other laboratory-based variations [74]. The AHA guideline recommends that NSE or serum S-100  $\beta$  protein should not be used alone to predict poor neurologic outcome (class III harm, LOE C-LD) [5••]. If obtaining a single serum NSE, day 3 values may be the most accurate for diagnosing poor outcome [75]. Serial sampling may also improve accuracy [76].

### Serum neurofilament light chain

The development of an ultrasensitive assay has prompted interest in serum neurofilament light chain as a predictor of poor outcome following cardiac arrest. In the TTM trial, serum neurofilament light chain was a more sensitive predictor of poor outcome than the neurological exam or electrophysiological assessments with comparable specificity [77••]. Target temperature may affect levels depending on the time-point tested.

## Neuroimaging

### Computed tomography (CT)

Reduced gray-white ratio at the level of the basal ganglia predicts poor outcome with variably low FPRs based on measurement technique and threshold [78–81]. Insufficient data are available to suggest a significant effect of TTM on CT imaging following cardiac arrest. The AHA guideline suggests that it may be reasonable to use a marked reduction in gray-white ratio on brain CT obtained within 2 h after cardiac arrest to

**Table 1. Suggested neuromonitoring for ECPR patients at key time-points**

Timing in reference to ECMO placement for ECPR	Purpose of assessment	Recommended measures
Pre-cannulation	<ul style="list-style-type: none"> <li>• To assess if there is severe anoxic brain injury (relative contraindication)</li> <li>• TTM eligibility</li> </ul>	<ul style="list-style-type: none"> <li>• *CT Head for edema</li> <li>• Quantitative pupillary exam for PLR and NPI</li> </ul>
Post-cannulation	<ul style="list-style-type: none"> <li>• Monitoring for significant neurological complications (stroke, hemorrhage, and seizures)</li> <li>• Neuro-prognostication</li> <li>• Brain-death declaration</li> </ul>	<ul style="list-style-type: none"> <li>• Serial neurological exam</li> <li>• Continuous EEG</li> <li>• CT head</li> <li>• Neuron-specific enolase</li> <li>• Somatosensory evoked potentials</li> </ul>
Post-awakening	Short- and long-term screening for cognitive, functional, neurological, and psychosocial deficits	<ul style="list-style-type: none"> <li>• RBANS or TICS</li> <li>• M-PSMS</li> <li>• M-IADL</li> <li>• mRS</li> <li>• CES-D</li> <li>• PCL-5</li> <li>• GAD-2</li> </ul>

*CES-D* Center for Epidemiological Studies-Depression, *ECMO* extracorporeal membrane oxygenation, *ECPR* extracorporeal cardiopulmonary resuscitation, *EEG* Electroencephalography, *GAD-2* generalized anxiety disorder, *M-IADL* The Lawton Instrumental Activities of Daily Living (IADL) Scale, *M-PSMS* Modified Lawton Physical Self-Maintenance Scale, *mRS* modified Rankin Scale, *NPI* Neurological Pupillary index, *PCL-5* post-traumatic stress disorder checklist—civilian, *PLR* pupillary light reflex, *RBANS* Repeatable Battery for Neuropsychological Status, *TICS* Telephone Interview for Cognitive Status, *TTM* targeted temperature management

\*Obtaining CT Head may not be possible due to hemodynamic instability in certain cases

predict poor outcome in patients not treated with TTM (class IIB, LOE B-NR), but makes no recommendations for patients treated with TTM [5••].

## Magnetic resonance imaging (MRI)

Neuronal injury on MRI is detected by diffusion-weighted imaging (DWI) and quantified by the apparent diffusion coefficient (ADC). Both qualitative measures of DWI abnormalities and quantified ADC thresholds have been reported as predictors of poor outcome following cardiac arrest, in either regional or global distributions [82, 83, 84•]. Methodological variance is partially responsible for the wide variation of reported FPRs for poor outcome. There are also concerns regarding interrater reliability when quantitative values are not obtained [85]. In addition, MRI changes following cardiac arrest are dynamic [86]. The preferred timing of MRI for prognostication is uncertain, but most experts advocate waiting 2–5 days following cardiac arrest. The influence of TTM on MRI-based prognostication is unknown, but some advocate for longer waiting periods prior to obtaining MRI in patients who undergo TTM [87•]. The AHA guidelines suggests that it may be reasonable to consider extensive restriction of diffusion 2–6 days following cardiac arrest in combination with other predictors to predict poor outcome (class IIB,

LOE B-NR) [5••]. Whether hypothermia has any effect on resting state neural networks, fractional anisotropy on diffusion tensor imaging or any metabolites measured via magnetic resonance spectroscopy is unknown.

## ECMO as a therapeutic agent after cardiac arrest

ECMO is an increasingly used technique providing cardiopulmonary support to patients with severe refractory cardiac and respiratory failure. Venous-arterial ECMO in the setting of cardiac arrest is used either as extracorporeal cardiopulmonary resuscitation (ECP) during cardiac arrest refractory to conventional cardiopulmonary resuscitation, or for post-cardiac arrest cardiogenic shock. There is a high incidence of neurological complications reported in patients requiring ECMO during or after cardiac arrest [88, 89••, 90]. Neuromonitoring would be appropriate pre-cannulation to identify the salvageable cases devoid of severe anoxic brain injury in cases where this is feasible, and post-cannulation to prognosticate comatose survivors and to potentially declare brain death when there is evidence for it (Table 1). Limited data exist regarding the predictive value of the different monitoring modalities in this setting.

### Neurological exam

During ECMO support, patients may undergo physical examinations per the standard procedure, restricted only by sedation and neuromuscular blockade. Comatose ECMO patients are thus, often-limited to pupillary assessments, and data is conflicting at best. Maekawa et al. suggested that pupil diameter on hospital arrival may be a key predictor of neurologic outcome in patients who went on to receive ECMO [91]. However, another study showed no differences in pupil diameter on arrival to the emergency room between survivors and non-survivors of ECMO for out-of-hospital cardiac arrest [92]. The authors did observe a positive pupillary reflex more frequently in after initiation of ECMO, and this was seen in significantly more survivors than non-survivors.

New automatic computerized devices such as the NPi-200 Pupillometer, which measures pupillary size and reactivity, have eliminated inaccuracies caused by interpreter reliability. One small study ( $N = 28$ ) has found the quantitative neurological pupillary index to be a useful early neuro-prognosticator in venous-arterial ECMO patients [93•].

### Electrophysiology (EEG and SSEP)

While there is very little data in adults, studies from critically ill neonates placed on ECMO post-hypoxic-ischemic encephalopathy provide some evidences that monitoring of electrical activity via EEG and SSEP may not be entirely accurate for patients during ECMO [94]. Data from neonates receiving ECMO have highlighted the fact that abnormalities in EEG background could be a result of ECMO and may resolve with time [95, 96]. The most abnormal EEG while receiving ECMO and EEG and



SSEP readings after decannulation have been shown to have the strongest predictive value for neurological prognosis [95]. The data is sparse in adults; there has been a recent small study examining EEG background ( $N=13$ ) and SSEPs ( $N=7$ ) in patients on VA ECMO [97•]. Only poor variability and absence of reactivity were associated with unfavorable neurologic outcome. Of the seven patients who received the SSEPs as well, all had poor outcomes, despite the presence of N20 response (4 normal, 3 delayed). However, based on the small sample size and the fact that no patients had absent N20 responses and, even when they were present, they were due to peripheral delays; the researchers urge caution when using EEG and SSEPs to prognosticate in patients receiving ECMO until the results of their study are better understood and validated (5).

## Neuroimaging

Choices for imaging techniques, as with physical examinations, are limited during ECMO support. Due to the ferrous properties of the ECMO pump and circuit, magnetic resonance imaging while receiving ECMO is contraindicated. In adults, cranial computed tomography (CT) is preferred but due to the difficulty of transporting patients receiving ECMO support [98], some ECMO patients only undergo CT after decannulation. Portable CT scanners have potential to make imaging more widely available. Studies looking at the predictive ability of CT in ECMO patients are sparse. One small study ( $N=20$ ) [92] showed that findings on brain CT just after ECMO and subsequent images may represent an important predictor for neurologic outcome. Further, all patients ( $N=4$ ) who had intracranial hemorrhage due to hypoxic brain damage on follow-up images died regardless of the initial CT findings. Growing clinical experience with ECMO has led to greater awareness about CT imaging pitfalls, including variable levels of flow assistance and cannulation strategies that all may potentially affect interpretation of imaging studies [99].

## Serum biomarkers

Plasma biomarkers have the potential to emerge as a leading monitoring tool to predict the neurological outcome for patients during ECMO. An ideal biomarker would have high sensitivity for detection of both ischemic and hemorrhagic injury, provide real-time information, and allow detection of injury at the cellular level that precedes cellular death [100]. Several biomarkers related to glial injury (glial fibrillary acidic protein (GFAP) and serum S-100  $\beta$ ), neuronal injury (NSE), and other markers of neuroinflammation (ICAM-5 and monocyte chemoattractant protein 1/chemokine (C-C motif) ligand 2 (MCP-1/CCL-2)) have been associated with a higher risk of neurological injury and death [100–102]. Similarly, serum S-100  $\beta$  may serve as an early indicator of cerebral complications, in particular, intracerebral hemorrhage [103]. In a more recent meta-analysis (17 papers containing 903 cases), high serum lactate level was associated with poor survival and poor neurological outcome in CA patients treated with ECMO [104•]. Lastly, elevated

concentrations of GFAP and ICAM-5 predicted abnormal neuroimaging [101]. While validation in larger studies is still required, these preliminary findings have suggested biomarkers mentioned above as potential indicators for obtaining further investigations (i.e., neuroimaging and non-invasive neuromonitoring) and for initiation of neuroprotective therapies.

### Brain death declaration

The American Academy of Neurology has outlined criteria for the determination of brain death [105]. Given the high reported mortality rates—and in particular, brain death—in patients treated with ECMO for cardiac arrest, a thorough understanding of the definition and determinations of brain death is critical. Despite the importance of the assessment of brain death, objective protocols for patients receiving ECMO are clearly lacking [106•]. Unfortunately, patients who require ECMO support often have physiologic conditions that might further challenge apnea testing. For patients being supported with venoarterial ECMO, pulsatile flow and blood pressures in the absence of significant doses of vasoactive agents might be too low as mandated by the AAN prior to attempting an apnea test. Various strategies have been proposed but have not reached universal consensus [107, 108]. Ancillary tests including continuous electroencephalographic (EEG) testing may be helpful when positive, but external electromagnetic energy sources like ECMO circuitry, may make conclusive interpretation of results difficult. Cerebral angiography or nuclear scanning may document the absence of cerebral blood flow, but such testing in patients receiving ECMO may be due to logistics [109•]. To compensate for the confounding influence of the inherent ability of the ECMO circuit not only to provide hemodynamic stability, but also more importantly, to maintain adequate oxygenation and normal blood carbon dioxide levels; some investigators have proposed modifications of ECMO flows and gas exchange during apnea testing. However, such experiences are limited to small series of patients [107, 108].

### Conclusion

With advances in therapeutics such as TTM and ECMO and effective public health campaigns, survival rates after cardiac arrest have increased significantly in the last decade. Despite such optimistic developments, withdrawal of life-sustaining therapy because of perceived poor neurological prognosis remained the most common cause of hospital death after cardiac arrest. Sedation continues to be the most critical confounder adversely affecting the reliability and the validity of measures traditionally being validated in the pre-TTM era for neuro-prognostication after cardiac arrest. Future studies are needed to examine the value of a multimodal prognostication scheme that includes novel biomarkers, quantitative measures of brain stem reflexes, and point-of-care cerebral perfusion monitors that allow optimization of blood flow after achieving a return of spontaneous circulation after cardiac arrest. Outcomes to test predictive abilities should integrate neurocognitive, functional, and psychological deficits along with survival.

## Compliance with Ethical Standards

### Conflict of Interest

Sachin Agarwal, Nicholas Morris, Caroline Der-Nigoghossian, and Teresa May each declare no potential conflicts of interest.

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### Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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