



## **BOX Trial: Oxygen Targets in Comatose Survivors of Cardiac Arrest**

### **Key Article**

Schmidt H, Kjaergaard J, Hassager C, et al. Oxygen targets in comatose survivors of cardiac arrest. *N Engl J Med*. Published online August 27, 2022.

### **Background**

- Hypoxic-ischemic brain injury is the leading cause of death in patients with ROSC after CA.
- During resuscitation, the brain is exposed to hypoxia along with reperfusion injury when ROSC is established.
- The potential pathophysiologic link between brain injury and oxygenation seems to occur in the early period after CA and ROSC and driven by reperfusion injury and tissue inflammation
- Patients who remain comatose after ROSC are intubated and initiated on mechanical ventilation with the administration of supplemental oxygen.
- In recent years a number of studies and trials have investigated both hyperoxia and hypoxia on mortality in patients with CA.
- In fact, two recent trials (HOT-ICU; ICU-ROX) did not show a difference in ventilator days between patients who received liberal vs restrictive oxygen targets. However, a subgroup analysis of the ICU-ROX trial suggested conservative O<sub>2</sub> treatment may be better.
- There remains clinical equipoise regarding oxygenation targets in patients who remain comatose after OHCA.

### **Objective**

- Evaluate whether a restrictive or liberal oxygen target was superior in patients who remain comatose from OHCA.

### **Methods**

- Investigator-initiated, open-label, randomized trial with 2-by-2 factorial design
- 2 tertiary cardiac arrest centers in Denmark
- Patients
  - Included
    - Adults aged 18 years or older
    - Comatose after OHCA of presumed cardiac etiology
  - Excluded
    - Unwitnessed asystole
    - Suspected intracranial bleeding or stroke
- Intervention(s)
  - General medical care
    - Patients received TTM to 36 degrees C x 24 hours, with 72 hours of active normothermia
    - Sedation with propofol/fentanyl for 24 hours, reduced during rewarming to assess neurologic status

- Randomization
  - Restrictive Target Group
    - PaO<sub>2</sub> 68-75 mm Hg
    - Initial FiO<sub>2</sub> set at 30% and adjusted to assigned target
  - Liberal Target Group
    - PaO<sub>2</sub> 98-105 mm Hg
    - Initial FiO<sub>2</sub> set at 60% and adjusted to assigned target
- Primary Outcome
  - Composite of death or discharge from the hospital with a Cerebral Performance Category of 3 or 4 within 90 days or at time of discharge.
- Secondary Outcomes
  - Plasma neuro-specific enolase levels at 48 hours
  - Death from any cause
  - 90-day scores on the Montreal Cognitive Assessment, mRS, and CPC
- Adverse Events
  - Bleeding
  - Infection
  - Arrhythmia
  - Electrolyte derangement
  - AKI with RRT
  - Seizures

## Results

- In total, 802 patients were enrolled from March 2017 – December 2021
  - 789 patients were included after exclusions for consent withdrawn and 1 patient who was randomized twice.
  - Restrictive Target Group: 394
  - Liberal Target Group: 395
  - Characteristics of patients were well balanced
- Oxygen Intervention
  - On arrival to the ICU, patients in both groups had similar PaO<sub>2</sub> and FiO<sub>2</sub> values
  - Separation between the groups was seen within 2-4 hours and remained there through the first 48 hours
  - Median duration of mechanical ventilation
    - Restrictive Target Group: 57 hours
    - Liberal Target Group: 61 hours
- Primary Outcome
  - Restrictive Target Group: 32%
  - Liberal Target Group: 33.9%
  - No statistical difference
  - Results consistent among subgroups and no interaction with BP groups from BOX Trial 1
- Secondary Outcomes
  - Death from any cause at 90 days
    - Restrictive Target Group: 28.7%
    - Liberal Target Group: 31.1%
  - NSE Levels
    - No difference

- Montreal Cognitive Assessment, mRS, and CPC
  - No difference
- AKI with need for RRT
  - No statistical difference
- Adverse Events
  - Most common were infection, bleeding, and seizures
  - No significant difference between the groups

#### **Limitations**

- Enrolled only patients with a presumed cardiac etiology of CA – a population with a high prevalence of CAD/ACS – generalizable to other causes?
- PaO<sub>2</sub>/FiO<sub>2</sub> ratio was higher in this trial than others – suggests that hypoxic respiratory failure was infrequent in this trial. For some, the spontaneous PaO<sub>2</sub> values were higher than target values without supplemental O<sub>2</sub>
- Limited by the number of patients who could be evaluated in person at 90 days
- Open-label

#### **Take Home Points**

- Authors found no difference in a composite outcome of death or severe disability at 90 days in OHCA patients randomized to a restrictive or liberal oxygen target.