BOX Trial: Blood-pressure targets in comatose survivors of OHCA

Key Article
Kjaergaard J, Møller JE, Schmidt H, et al. Blood-pressure targets in comatose survivors of cardiac arrest. N Engl J Med. Published online August 27, 2022:NEJMoa2208687.

Background
- After cardiac arrest, goal-directed post-resuscitation care often targets normalized perfusion pressure by targeting a mean arterial pressure, often > 65 mmHg
- Observational data suggest that post-ROSC MAP to ensure adequate blood flow to the postanoxic brain is at least 75mmHg, but guidelines suggest that a MAP of 65mmHg should be targeted.
- High-quality data is limited, but three previous RCTs (Ameloot, 2019; Jakkula 2018; Grand, 2020) have tested high vs. low MAP including:
  - Ameloot (2019) Euro Heart Journal: Targeting a higher MAP (85-100) vs. 65 mmHg in post-CA patients was safe and improved cerebral oxygenation but did not improve the extent of anoxic brain damage or neurological outcome.
  - Jakkula (2018) ICM: Targeting a MAP 65-75 vs. 80-100 mmHg was feasible during post-resuscitation intensive care but did not affect the NSE concentration at 48 h after cardiac arrest, nor any secondary outcomes.
  - Grand (2020) EHJ Acute CV Care: Double-blind trial of 50 patients found a MAP target of 72 mm Hg compared to 65 mm Hg did not result in improved biomarkers of organ injury (markers of endothelial integrity (soluble thrombomodulin) brain damage (neuron-specific enolase) and renal function.

Objective
- The primary objective was to test whether a MAP of 63 vs. 77 mmHg would be superior in preventing death or severe anoxic brain injury among comatose survivors of OHCA.

Methods
- Randomized clinical trial, 2x2 factorial design
  - MAP target: 63 vs. 77 mmHg (double-blind intervention)
  - O2 target: restrictive or liberal oxygenation (open-label intervention)
- Location: two medical 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)

- o 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
- o Experimental arm(s)
    - ▪ Clinical staff, investigators, patients, and outcome assessors were unaware of the assigned blood-pressure targets, but were told to target a MAP of 70 mmHg
        - • Actual BP targets were achieved by assigning patients to an electronic module that was set to show either 10% higher or lower value than the actual MAP, so clinicians would actually achieve 63 vs. 77 mmHg groups.
    - ▪ Resuscitation to MAP target of 70 mmHg was achieved using a 3-stage approach, starting with IV fluids to achieve a CVP of 10 mmHg, norepinephrine infusion (dopamine as second line pressor)
    - ▪ Other hemodynamics were not altered (CVP, cardiac output, etc.)
- • Primary Outcome - Peter
    - o 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
    - o Death from any cause within 90 days
    - o Time to renal-replacement therapy
    - o Neuron specific enolase levels at 48 hours after randomization
    - o Multiple different cognitive scores at 3 months
- • Sample size was chosen to detect a 10% mortality difference between treatment groups.

Results
- • In total, 802 patients were enrolled from March 2017 – December 2021
    - o 789 patients were included after exclusions for consent withdrawn and 1 patient who was randomized twice.
    - o High BP Group: 393 patients
    - o Low BP Group: 396 patients
- • In general, the trial appears to have achieved a MAP difference of 10.7 points starting at randomization – 65 vs. 75 mmHg (randomization usually took place in ICU, not ED).
    - o Time to randomization (from supplemental file) was approximately 150 minutes or 2.5 hours from cardiac arrest in both groups
- • Patient characteristics
    - o Median age
        - ▪ High BP Group: 63 years
        - ▪ Low BP Group: 64 years
    - o Most frequent type of arrest: Shockable Rhythm (VT/VF)
        - ▪ High BP Group: 86%
        - ▪ Low BP Group: 84%
    - o Witnessed arrest:
        - ▪ High BP Group: 86%
        - ▪ Low BP Group: 84%
    - o Bystander CPR
        - ▪ High BP Group: 88%

- - - Low BP Group: 87%
    - Over 40% in each arm had a post ROSC STEMI, > 90% of all patients had a post-ROSC cath. Initial lactate levels in both groups were approximately 6 mmol/dL .
- There was good separation between mean BP in 2 groups using the randomized assignment of BP monitors. (approximately 10 mmHg)
- Vasopressor use to achieve goals was the same in both groups
- Primary Outcome
    - High BP Group: 34%
    - Low BP Group: 32%
    - Not statistically significant
- No difference in any of the secondary outcomes, including
    - Death from any cause at 90 days
        - High BP Group: 31%
        - Low BP Group: 29%
    - Acute kidney injury with renal replacement therapy: 10% in both groups
    - 3-month CPC or other neurologic assessment scores
    - Or Neuron-specific enolase (biochemical marker of neuronal injury)
- No difference in any of the recorded complications (infection, arrhythmia, bleeding, metabolic disorders, or seizures).

Limitations
- Did not achieve the separation of 14 points (goal was MAP 63 vs. 77) that was initially targeted
    - Authors argue that 65 vs. 75 is still clinically significant, which is probably true
- BP targets were not titrated based on degree of anoxic injury – perhaps those with worse anoxic injury need higher BP targets?
    - Would have been interesting to know the duration of CPR prior to ROSC
- Long-term neurologic outcomes were only measured in 65% of surviving patients – limited by the COVID-19 pandemic.

Take Home Points
- A MAP of 65 vs. 75 mm Hg did not result in a significant difference in death or severe disability after OHCA from a likely cardiac cause.