**Experiences with AKI Clinical Trial Design**

Sudarshan Hebbar MD
Chief Medical Officer
CalciMedica, Inc.

The KOURAGE trial has been designed to test the efficacy and safety of Auxora™ for the treatment of patients with acute hypoxemic respiratory failure and severe acute kidney injury.[1] The study design prognostically and predictively enriches for patients who are at highest risk of adverse outcomes and most likely to respond to treatment with Auxora™.[2] Prognostic and predictive enrichment strategies are strongly encouraged when designing therapeutic trials in AKI as they minimize the heterogeneity of an AKI study population and enhance the detection of an efficacy signal.[3] The selection of efficacy endpoints depends on whether the trial is a preventative or treatment trial and the stage of drug development.[4] The KOURAGE primary endpoint (days alive, ventilator free and kidney replacement free) is appropriate for a late stage treatment trial of a drug developed to mitigate the severity of organ failure. The usual endpoint used in late stage AKI trials is MAKE-90. The MAKE-90 endpoint, however, needs reevaluation because it may not be appropriate for a preventative trial, there is considerable variation on how it is defined, it does not hierarchically rank the components, and the interpretation of results is highly dependent on the baseline condition of the patient.[5,6] Does a reduction in GFR provide the same harm to a patient as does dying? Does a 25% reduction in GFR portend the same prognosis for a patient with a baseline GFR of 100 mL/min compared to one with a GFR of 45 mL/min?

While there have been much attention paid to the design of an AKI trial, there has been less focus on the obstacles to conducting the trial. Defining AKI using a change in creatinine depends on the baseline creatinine, but that value is frequently missing. The lack of a baseline creatinine makes conclusions about the effect of therapy on preserving GFR for an individual patient suspect. Imputation of a baseline creatinine using GFR formulas lacks objective rigor and is biased if race is a variable. Urine output is also used to define AKI. A decrease in urine output is important for the accurate identification of severe AKI,[7,8] but health systems have instituted policies hindering its accurate collection, even in the ICU. Many recent studies of AKI are reporting results without analyzing urine output; their findings have limitations.[9,10,11] Finally, there is no definition of AKI for patients with chronic kidney disease. Consequently, these patients are often excluded from AKI trials despite being the population in greatest need of a therapy. Study manuscripts should report how these obstacles were overcome when conducting the trial.

**References**

1. https://clinicaltrials.gov/study/NCT06374797?cond=AKI&intr=auxora&rank=1
2. Chawla, Lakhmir S., et al. "Inhibition of Calcium Release-Activated Calcium (CRAC) channels to Treat Acute Kidney Injury: Design and Rationale of the KOURAGE study." *American Journal of Nephrology* (2025).

3. Lazzareschi, Daniel, et al. "Overcoming barriers in the design and implementation of clinical trials for acute kidney injury: a report from the 2020 Kidney Disease Clinical Trialists meeting." Nephrology Dialysis Transplantation 38.4 (2023): 834-844.
4. Zarbock, Alexander, et al. "Recommendations for clinical trial design in acute kidney injury from the 31st acute disease quality initiative consensus conference. A consensus statement." Intensive Care Medicine 50.9 (2024): 1426-1437.
5. Maeda, Akinori, et al. "Heterogeneity in the definition of major adverse kidney events: a scoping review." Intensive Care Medicine 50.7 (2024): 1049-1063.
6. Fuhrman, Dana Y., et al. "Major adverse kidney events as an endpoint in acute kidney injury trials: is it time for a RE-MAKE?." Intensive Care Medicine 50.10 (2024): 1723-1724.
7. Kellum, John A., et al. "Classifying AKI by urine output versus serum creatinine level." Journal of the American Society of Nephrology 26.9 (2015): 2231-2238.
8. Bianchi, Nathan Axel, et al. "Association of oliguria with acute kidney injury diagnosis, severity assessment, and mortality among patients with critical illness." JAMA network open 4.11 (2021): e2133094-e2133094.
9. Landoni, Giovanni, et al. "A randomized trial of intravenous amino acids for kidney protection." The New England journal of medicine 391.8 (2024): 687-698
10. Wilson, F. Perry, et al. "Electronic health record alerts for acute kidney injury: multicenter, randomized clinical trial." bmj 372 (2021).
11. Li, Ting, et al. "Automated electronic alert for the care and outcomes of adults with acute kidney injury: a randomized clinical trial." JAMA network open 7.1 (2024): e2351710-e2351710.