Title: Evaluation of the hemodynamic tolerance of potassium canrenoate in brain-dead organ donors: randomized controlled clinical trial "CANREO-PMO" NCT04714710

Statistical Analysis Plan
Version 1.0 June 17, 2025
Validated before partial database lock
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Study outcomes

Primary outcome

Primary outcome will be a hierarchical composite outcome, as described by Felker et al [1], ranked in descending order of clinical importance:

A/ Cardiocirculatory arrest before organ procurement,

B/ Inability to perform renal procurement,

C/ Average hourly dose of epinephrine/norepinephrine between randomization and departure to the operating room (considered as an ordinal variable with 10 levels : 0, 0-0.5, 0.5-1, 1-1.5, 1.5-2, 2-3, 3-4, 4-5, 5-10, >10 mg/h),

D/ Average volume of colloids/crystalloids between randomization and departure to the operating room.

The following algorithm was used to compute the primary outcome (ranking variable):

		Rank
A/ Cardiocirculatory arrest before organ procurement	→ Yes	$(n_1 + 1) / 2$
↓ No		
B/ Inability to perform renal procurement	→ Yes	$(n_2 + 1) / 2 + n_1$
↓ No		
C/ Average hourly dose of epinephrine/norepinephrine (10 levels : 0, 0-0.5, 0.5-1, 1-1.5, 1.5-2, 2-3, 3-4, 4-5, 5-10, >10 mg/h) D/ Average volume of colloids/crystalloids	→	Ranking will be assigned based on the level of average hourly dose of epinephrine/norepinephrine (from highest to lowest), and within each category, based on the average volume of colloids/crystalloids (from highest to lowest)

n_1: number of subjects with cardiac arrest before organ procurement; n_2: number of subjects with inability to perform kidney procurement.

Note: The higher the rank, the better the outcome. Ideally: no cardiac arrest, no inability to perform kidney procurement, no norepinephrine/epinephrine administration, and no or minimal volume of crystalloids/colloids infusion.

Secondary outcomes

Here is the list of all secondary outcomes of this study, ranked in order of importance (from most to least important):

Table 1: Secondary outcomes and importance order

Importance Order	Secondary Outcome
1	Graft function at 3 months
2	Return to dialysis within 3 months after transplantation and/or eGFR < 20 mL/min/1.73m² at 3 months
3	Vital status of the kidney graft recipients at 3 months
4	Graft function at 1 year
5	Graft survival at 1 year
6	Vital status of the kidney graft recipients at 1 year
7	Graft function at 3 years
8	Graft survival at 3 years
9	Vital status of the kidney graft recipients at 3 years
10	Graft function at 10 years
11	Graft survival at 10 years
12	Vital status of the kidney graft recipients at 10 years

Note : secondary outcomes 7 to 12, assessed at 3 and 10 years, will not be available at the time of the initial analyses. The study will continue in order to collect these data, and these outcomes will be analyzed later.

Statistical analysis

Sample size consideration

We hypothesize that no cardiocirculatory arrest will occur before organ harvesting and that all organ procurement will be performed. We expect a mean hourly norepinephrine/epinephrine dose of 1.18 mg/hour in the control group vs 1.42 mg/hour in the canrenoate group (+20%), with a common SD of 0.92 mg/hour. Similarly, we anticipate a mean colloids/crystalloids

volume of 1 L in the control group vs 1.2 L in the canrenoate group (+20%), with a common SD of 2 L. A total of 36 randomized patients are required to achieve at least 80% power at a two-sided alpha level of 5% to demonstrate the non-inferiority of canrenoate use with a non-inferiority margin of 60%, using a parametric Student's t-test. If there is 5% cardiocirculatory arrest, the power will still be >80%.

General considerations

All analyses will be performed using R software version 4.1.2 (the R foundation for Statistical Computing).

Population analyzed

Intention-to-treat (ITT) population: all patients included will be analyzed based on the initial treatment assignment.

Per-protocol (PP) population: all patients included without major protocol violations. Major protocol violations will be defined prior to any analysis and blinded to treatment.

As treated (AT) population: all patients will be analyzed based according to the treatment actually received.

The primary analysis will focus on the AT population. Sensitivity analyses will be performed on ITT and PP populations.

Descriptive statistics

Continuous variables will be described by the number of non-missing values, mean and standard deviation or median and interquartile range (1st quartile and 3rd quartile), as appropriate. Categorical variables will be summarized by the observed frequencies and the percentages relative to the total number of non-missing items.

Description of statistical analysis of primary and secondary outcomes

Graft function will be defined by the GFR value estimated using the CKD-EPI formula. In the event of patient death, a GFR value of 0 mL/min/1.73 m² will be assigned. In the event of return to dialysis, a GFR value of 5 mL/min/1.73 m² will be assigned. Graft survival will be defined as the patient being alive without return to dialysis.

To handle the multiple testing, outcomes will be analyzed using a hierarchical testing procedure until the p-value equals or exceeds 0.05 [2, 3], the primary outcome being the most important outcome, followed by the secondary outcomes ranked according to the importance order shown in Table 1 (page 2).

Analysis of the primary outcome

The primary outcome is a hierarchical composite outcome. It will be analyzed using a Student's t-test applied to the rank variable derived from the hierarchical ranking of patients. This parametric approach is necessary to establish non-inferiority, which requires a predefined non-inferiority margin based on a distance measure relative to a parameter.

To improve interpretability, the primary outcome will also be analyzed using the win ratio method. Furthermore, each component of the primary outcome will be summarized individually. For each binary component, the proportion of events in each group and the difference in proportions between groups will be reported with its 95% confidence interval (CI). For each continuous component, the mean value will be reported for each group, along with the corresponding mean difference and its 95% CI. In case of non-normality, the median value for each group and the median difference (Hodges-Lehmann estimate) with corresponding 95% CI will be presented.

If clinically meaningful differences are observed in baseline characteristics between the two groups, additional adjusted analyses will be performed. Linear regression or proportional odds model will be used for continuous components, and logistic regression for binary components.

Analysis of the secondary outcomes

Secondary outcomes listed in Table 1 (page 2) will be analyzed with Student's t-test or Mann-Whitney test for continuous outcomes and chi-square test for categorical outcomes, as appropriate. Results will be presented as means, medians, or proportions for each group, along with the corresponding between-group differences and their 95% CIs. Adjusted analyses will be performed, if necessary, using the same approach as described in the 2nd paragraph of the "*Analysis of the primary outcome*" section.

Reference

[1] Felker GM, Maisel AS. A global rank end point for clinical trials in acute heart failure. Circ Heart Fail 2010;3:643–6.
[2] Harrington D, D'Agostino RB, Sr, Gatsonis C, Hogan JW, Hunter DJ, Normand ST, et al. New guidelines for statistical reporting in the journal. N Engl J Med. 2019;381:285–6.
[3] Dmitrienko A, Tamhane A, Bretz F. Multiple Testing Problems in Pharmaceutical Statistics. CRC/Taylor & Francis; 2010.

Version history

Version	Date	Nature of modification	Author
1.0	June 17, 2025	Document creation	Kevin Duarte