Double-blind Placebo-Controlled Randomized Clinical Trial of Mineralocorticoid Receptor Blockade With Eplerenone After Renal Transplantation : Effect on Graft Function at 3 Months.
EPURE TRANSPLANT

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EPURE Transplant Statistical analysis plan
14/06/2023
Validated before database lock
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Study outcomes

Primary outcome

Graft function at 3 months assessed by measured GFR (mL/min/1.73m²) using iohexol clearance will be the primary outcome of this study.

Secondary outcomes

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

Table 1: Secondary outcomes and importance order

Importance Order	Secondary Outcome
1	eGFR at 1 year
2	Time delay for graft recovery assessed by the proportion of patients with immediate (defined by a serum creatinine < 30 mg/L at 7 days post-KT), slow (defined by a serum creatinine > 30 mg/L at 7 days post-KT without dialysis requirement), or delayed graft function (defined by the necessity of one or more dialysis sessions during the 7 days following KT)
3	Proportion of patients with either dialysis dependency or a GFR < 30 mL/min/1.73m² at 3 months
4	Time delay for graft recovery assessed by the proportion of patients with a DGF defined by the necessity of one or more dialysis sessions during the 7 days following KT
5	Length of hospital stay for the KT (days)
6	Twenty-four hour proteinuria levels at 3 months
7	Twenty-four hour microalbuminuria levels at 3 months
8	Graft survival at 1 year
9	Patient survival at 1 year
10	Occurrence of biopsy-proven acute rejection in the first 3 months following KT
11	Occurrence of hyperkalemia > 6 mmol/L during the first week following KT
12	eGFR at 3 years
13	Graft survival at 3 years
14	Patient survival at 3 years

DGF: delayed graft function, KT: kidney transplantation; GFR: glomerular filtration rate.

Statistical analysis

Sample size consideration

According to French statistical data (https://www.agence-biomedecine.fr/annexes/bilan2016/donnees/organes/06-rein/synthese.htm), the mean eGFR at 3 months among patients receiving a kidney graft from an ECD is 42 mL/min. Inclusion of 126 patients will allow identifying of a difference of 7 mL/min/1.73m² between the two groups (42 mL/min/1.73m² in the placebo group and 49 mL/min/1.73 m² in the eplerenone

group), with a standard deviation of 14 mL/min, a two-sided alpha risk of 5%, and a beta risk of 20% (power 80%). Since it is anticipated that 5% of patients could be included but not randomized or could withdraw their consent, we will target the inclusion of 132 patients.

General considerations
All analyses will be performed using R software version 4.3.0 (the R foundation for Statistical Computing).

Continuous variables
Continuous variables will be described by the number of non-missing values, mean and standard deviation. The normality of the distributions will be assessed. In case of violation of normality, the continuous variables will be described by the median and interquartile range (1^{st} quartile and 3^{rd} quartile).

Categorical variables
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
As per modified intention to treat analysis, every randomized patient who will undergo transplantation will be included in the analysis of primary and secondary outcomes.
As indicated in the protocol, for the primary endpoint, if the patient died within 3 months of randomization, a GFR value of zero at 3 months will be assigned. If the patient has returned to dialysis with a residual diuresis less than or equal to 250 ml/day, a GFR value of 5 mL/min will be assigned.
In patients with invalid measurement of GFR using iohexol clearance at 3 month, estimated GFR (CKD-EPI formula) will be used.

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

Analysis of the primary outcome
The primary outcome, which is to compare the mean measured GFR between the two groups, will be analyzed by a Student's t-test for independent samples, after verifying the normality of GFR distribution in each group and mean difference between groups in GFR will be provided along with its confidence interval. In case of non-normality, the non-parametric Mann-Whitney test will be used and median difference (Hodges-Lehmann estimate) with 95% confidence interval will be presented. An analysis adjusted on stratification factors will then be performed to avoid clustering effects arising from stratification [3].

Analysis of the secondary outcomes
Secondary outcomes listed in Table 1 (page 1) will be analyzed with Student's t-test or Mann-Whitney test for continuous outcomes and chi-square test for categorical outcomes, and differences will be presented as mean difference, median difference (Hodges-Lehmann estimate), or relative risk with 95% confidence intervals, as appropriate.
In the event of clinically significant differences between baseline characteristics of the patients of the two groups, possibly observed despite randomization due to the moderate number of patients in this trial, some explanatory analyses adjusted for these parameters and

on stratification factors will be performed and presented in the publication. Linear regression will be used for continuous variables and logistic regression for dichotomous variables.

In a supplementary analysis, per-protocol analysis will be performed.

Replacement
To account for the specific context of renal transplantation, patients who did not undergo renal transplant, who had early transplant nephrectomy (arterial or venous thrombosis of the graft) or could not have iohexol clearance measurements (p.e. medical counterindication for iohexol clearance measurements, unavailable to attend due to Covid lockdown) were replaced.

The results of the trial will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) Statement.

Reference

[1] Harrington, D. et al. New guidelines for statistical reporting in the journal. N. Engl. J. Med. 381, 286 (2019).
[2] Dmitrienko A, Tamhane A, Bretz F. Multiple Testing Problems in Pharmaceutical Statistics. CRC/Taylor & Francis; 2010.
[3] Kahan BC, Morris TP. Reporting and analysis of trials using stratified randomization in leading medical journals: review and reanalysis. BMJ. 2012;345:e5840.