ALCHEMIST

ALdosterone antagonist Chronic HEModialysis Interventional Survival Trial

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Statistical Analysis Plan

SAP version: Final version

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History of previous versions		
Version	**Date**	**Reason for the update**
V1.0 (version 0)	01/23/2018	Original version (statistical paragraph of protocol "2012-002856-18 ALCHEMIST V16 du 24.10.2017.pdf")
V1.1 (version 0)	03/01/2021	Original version (statistical paragraph of protocol "ALCHEMIST V18.0e du 15.10.2019 english final.pdf", updated number of subjects)
V1.2 (version 0)	03/15/2021	Original version (after meeting revision)
V1.3 (version 0)	03/21/2022	Original version (after meeting revision, subgroups identification)
V1.4 (version 0)	06/30/2023	Original version (protocol updated and after meeting revision) hierarchical testing strategy, adjustment and explanatory analysis
V1.5 (version 0)	08/25/2023	Original version (after meeting revision)
V1.6 (version 0)	09/07/2023	Original version (after meeting revision)
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Abbreviations

ACE inhibitors: angiotensin-converting enzyme (ACE) inhibitors

AE: Adverse event

ARB: Angiotensin receptor blockers

Chronic ESRD: Chronic end-stage renal disease

CRF: Case report form

CV: Cardiovascular

HD: Haemodialysis

MACE: Major cardiovascular events

MI: Myocardial infarction

NSAID: Non-steroidal anti-inflammatory drug

SAE: Serious adverse event

ACS: Acute coronary syndrome

Introduction

The purpose of this detailed statistical analysis plan is to describe precisely and unambiguously the planned statistical analyses to be carried out on the study database to support the completion of the Clinical Study Report (CSR).

All planned analyses identified in the protocol and in this SAP will be performed only after the formal database lock. A blinded data review meeting will be held prior to the database lock and completion of the final analyses. In addition, no database may be locked, random code unblinded, or analyses completed until this SAP has been approved.

Key statistics and study results will be made available to the Steering Committee following the database lock and prior to completion of the final CSR.

Any post-hoc exploratory analyses completed to support the planned study analyses, which were not identified in this SAP, will be documented and reported in appendices to the CSR. Any results from these unplanned analyses will also be clearly identified in the text of the CSR.

1 Study rationale and objectives

Chronic kidney disease (CKD) is a public health priority. The latest European data show an incidence of end-stage renal disease (ESRD) requiring renal replacement therapy of 118 per million inhabitants/year, a prevalence of 630 per million. The unadjusted mortality rate is 29% at 2 years and 52% at 5 years. ESRD is associated with increased cardiovascular (CV) morbidity and mortality (2 to 10 times that of a population with normal renal function). Heart disease is the leading cause of mortality in patients on haemodialysis (HD) (42% of total mortality). Despite these alarming observations, this syndrome remains the poor relation of CV prevention. Very few treatments are evidence-based and CKD patients on HD are usually excluded from CV prevention trials. Aside from two positive studies among ESRD HD patients with heart failure and severely impaired left ventricular ejection fraction (stages III-IV) using renin angiotensin aldosterone system (RAAS) blockers (beta-blocker carvedilol, or a combination of angiotensin converting enzyme inhibitor (ACE-I) with an angiotensin II receptor antagonist (ARA-II) telmisartan), two morbidity-mortality studies developed by the CIC-P Nancy, the designer of the present project, and specifically including ESRD HD patients, have showed on the one hand that a statin had no effect and, on the other, that an ACE-I had a positive effect (undersized study, generating a trend of efficacy). Another study conducted in HD diabetics showed that another statin had no effect. These limited and inconclusive findings make further studies by the pharmaceutical industry unlikely in the coming years. In order to avoid that HD patients, often excluded from CV morbidity-mortality trials, remain without evidence-based therapeutic resources and continue to present unacceptable CV morbidity and mortality rates, institutionally-sponsored trials are needed. Our group has significant experience in morbidity-mortality trials in HD.

Clinical and experimental data suggest that RAAS blockade with ACE-I or ARA-II can limit atherosclerosis and CV morbidity and mortality, independently of blood pressure reduction, at least in subjects at high cardiovascular risk without severe renal impairment. In non-dialysed patients with heart failure, three international controlled trials showed a reduction in cardiovascular morbidity and mortality induced by aldosterone antagonists (spironolactone and eplerenone). Our group participated in the design, conducting and publication of these three studies. The beneficial effects of aldosterone antagonists involve cardiovascular remodelling, including collagen synthesis, as well as effects on endothelial and immune functions. A recent randomised controlled trial conducted in early-stage CKD showed that adding spironolactone to ACE-I or ARBs reduces left ventricular mass and arterial stiffness, both of which are independent predictors of cardiovascular events

in patients with ESRD. Most clinicians are reluctant to use aldosterone antagonists because of the risk of hyperkalaemia. However, recent studies have demonstrated the safety of spironolactone in anuric ESRD HD patients.

Our study aims to determine the safety and efficacy of spironolactone on the reduction of cardiovascular events among ESRD HD patients, in comparison to placebo.

1.1 Primary objective

The primary objective is to determine the effects of spironolactone in comparison to placebo on a composite endpoint combining cardiovascular events of interest (major cardiovascular events and cardiovascular death). The primary endpoint is the time to onset of the first adjudicated expanded MACE event, i.e.:

- non-fatal myocardial infarction (MI) acute coronary syndrome,
- hospitalisation for heart failure,
- non-fatal stroke,
- or CV death.

Whenever a first event occurred, blinding is maintained and treatment continued until the end of the trial, and the patient continued to be followed as per the protocol.

MACE and death events are adjudicated by an independent blinded clinical event adjudication committee. The procedures and event definitions are described in an adjudication charter.

1.2 Secondary objectives

Part1

Following a hierarchical strategy of statistical tests including the primary endpoint, the secondary objective is to determine the effects of spironolactone versus placebo on the composite win ratio endpoint of: 1. all-cause mortality; 2. time to cardiovascular event (hospitalisation for heart failure, or non-fatal myocardial infarction, or non-fatal acute coronary syndrome or stroke) at 2 years using the Finkelstein and Schoenfeld method.

Part2

Additional secondary objectives will be considered for hypothesis generation:

a) mortality rate from non-CV causes
b) the cumulative rates of the composite outcome of non-fatal primary outcome events (hospitalisation for heart failure or non-fatal MI or acute coronary syndrome or stroke) and occurrence of
    i. All-cause death from any cause,
    ii. CV death
    iii. non-CV cause
c) cardiovascular event-free survival: survival without non-fatal MI and acute coronary syndrome, hospitalisation for heart failure, non-fatal stroke, or resuscitated cardiac arrest
d) incidence of procedures related to stenosis or thrombosis of the vascular access for HD
e) incidence of coronary or peripheral revascularisation (including lower-limb amputations

f) blood pressure (pre- and post-dialysis) and its inter-visit variability [Rossignol P, Cridlig J, Lehert P, Kessler M, Zannad F. Visit-to-visit blood pressure variability is a strong predictor of cardiovascular events in hemodialysis: insights from FOSIDIAL. Hypertension. 2012 Aug; 60(2):339-46. doi: 10.1161/HYPERTENSIONAHA.111.190397. Epub 2012 Jul 9.]

g) Occurrence of complete arrhythmia by atrial fibrillation.

h) incidence of hyperkalaemia > 6 mmol/l;

The following objectives and ancillary studies will be analysed in dedicated SAP:

i) estimation of the effect of treatment on the quality of life of patients with this dual pathology: CKD in HD and established cardiovascular pathology,

Part3: Ancillary studies

j) Creation of a biological collection for subsequent biomarker studies (serum and DNA libraries),

k) Post-study, mortality and cardiovascular morbidity assessed 3, 5 and 10 years after the end of the double-blind follow-up period, by consulting national epidemiological registers.

A health economics ancillary study will complete this project.

1.3 Experimental design and studied population

1.3.1 Study outline

This is a randomised, controlled, double-blind, multicentre, parallel-group trial. After an open-label run-in period of one month under 25 mg spironolactone every second day (administered in practice after the HD session, three times a week), patients was randomised (spironolactone vs. placebo), and undergo titration over one month, with a maximum single dose of 25 mg/day. A pre-specified algorithm for the management of the risk of incident hyperkalaemia was followed, including dose adjustments, temporary discontinuation of the study treatment, in addition to the usual dietary measures, and the use of chelating resins and low-potassium dialysis baths.

Serum potassium levels was measured at the beginning of each session (3 times per week) over 2 months, and thereafter according to the titration algorithm data (in addition to usual follow-up, including serum potassium monitoring every two weeks), and during each visit of the protocol. Patients was followed for 2 years on average.

A Steering Committee (chaired by the coordinator, and comprised of nephrologists, cardiologists, pharmacologists, a statistician methodologist), an Oversight Committee and a Critical Events Adjudication Committee was planned.

1.3.2 Pre-specified algorithm for treatment administration and dosage

The selected dosages were based on literature data: satisfactory tolerance particularly in terms of serum potassium in patients on haemodialysis, choice of dosages similar to those with proven efficacy in cardiac failure patients (RALES), but slightly lower in light of the kidney failure.

Spironolactone was initially be administered at a single dose of 25 mg every second day administered in practice after the dialysis session, three times a week. Serum potassium levels were measured 3 times per week after initialisation of the

treatment throughout the entire run-in period of one month. Patients were excluded prior to randomisation if serum potassium is greater than or equal to 5.5 mmol/l on two occasions during the run-in or on the day of randomisation.

After randomisation, the dose was increased to a single dose of 25 mg/day by controlling serum potassium 3 times a week for one month, and thereafter every 3 months, in addition to usual follow-up, which includes at minimum performing a plasma ionogram every two weeks. Changes in treatment dosage of the trial and related serum potassium levels was collected in the case report form, without the need of an additional visit.

Dose adjustments during the course of randomisation: according to a proven algorithm in the EPHESUS and EMPHASIS-HF studies.

DOSE TITRATION ALGORITHM **The target dose is 25 mg/d**	
Pre-dialysis Serum Potassium (K^+) (mmol/L),	Dose adjustment or maintenance
<5.0	Increase in dose (if target dose not reached): • If the current dose is 25 mg every second day (administered in practice after the session, three times a week): increase to 25 mg/d.
5.0 – 5.4	CONTINUE WITH THE CURRENT DOSE (no adjustment)
≥5.5	LOWERING OF THE DOSE: • If the current dose is 25 mg/day, reduce to 25 mg every second day (administered in practice after the session, three times a week) • If the current dose is 25 mg every second day (administered in practice after the session, three times a week), temporary suspension of the treatment → retest serum potassium levels before the next dialysis and proceed as follows: ∗ If serum K^+ <5.5, resume study treatment at a dose of 25 mg every second day (administered in practice after the session, three times a week) ∗ If serum K^+ ≥5.5, temporary suspension of study treatment and retest serum potassium before the next dialysis

In parallel, in the event of hyperkalaemia deemed clinically significant by the investigator, the latter will follow the usual care protocols from his/her centre (intensification of dietary measures, use of chelating resins and low-potassium dialysis baths).

1.3.3 Randomization and blinding

The randomisation list was centralised and generated by the Biostatistics department of the Hospices Civils de Lyon. Randomisation was stratified on the centre, to ensure a balanced distribution of confounding factors between arms and between centres. After the run-in period, investigators were need to connect to the CSOnline electronic case report form of the study and randomize their patients. Treatment was automatically assigned following the pre-established randomization list. The allocation ratio was 1:1 between the two groups.

Treatment vials were indistinguishable, therefore, this is double blinded study.

1.3.4 Sample size determination

Assuming the following conditions:

- An annual event probability of events of 0.18 in the placebo arm (corresponding to an incidence of 19.84 per 100 person-years)
- A 30% reduction of this annual event probability in the spironolactone arm (active treatment), hence a probability of 0.126 (corresponding to an incidence of 13.46 per 100 person-years)
- A statistical power of 80% (β = 20%)
- A bilateral test with a type-1 error rate α of 5%
- A premature study discontinuation rate (early drop-out) of 10%

A total number of **750 randomised patients (375 per arm)** to follow over 2 years in average is required to analyse the treatment effect with an exponential survival model. Considering early drop-out of 10% before randomisation, **825 patients** should be included at run-in phase.

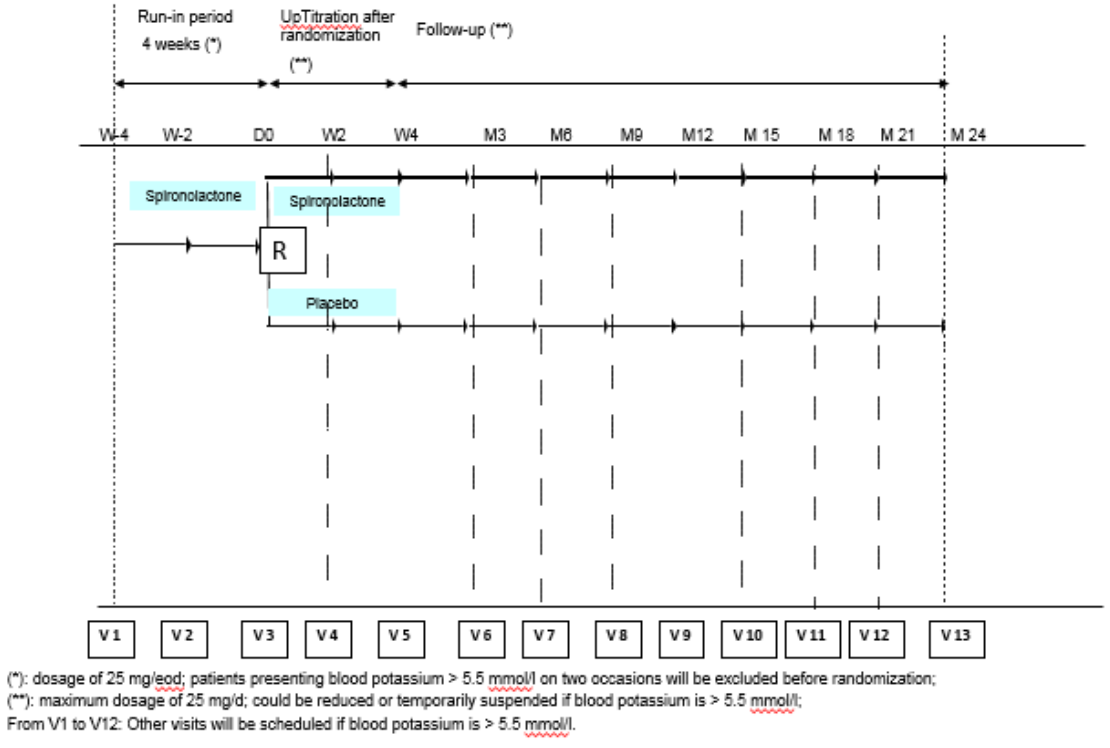
1.3.5 Chronological sequence

Eligible patients having signed the consent form participate in the one-month run-in phase after which they were randomised conditional to the absence of hyperkalaemia ≥ 5.5 mmol/l on two occasions or on the day of randomisation or of serious adverse events.

The included and randomised patients participate in the study for a duration of 2 years on average, the latter of which can be amended by the Steering Committee in light of the rate of event occurrences. The study was completed when the number of incidents necessary for attaining a sufficient power has been observed. Blinding was lifted only in the case of a serious adverse event in which care management may be modified according to the treatment received by the patient: spironolactone/placebo; patients were followed until the end of the study.

Figure 1: Scheme of the study

Figure 1: ALCHEMIST trial design



(*): dosage of 25 mg/eod; patients presenting blood potassium > 5.5 mmol/l on two occasions will be excluded before randomization;
(**): maximum dosage of 25 mg/d; could be reduced or temporarily suspended if blood potassium is > 5.5 mmol/l;
From V1 to V12: Other visits will be scheduled if blood potassium is > 5.5 mmol/l.

Summary table of visits.

	Visit 1 W-4	Visit 2 W-2	Visit 3 D0	Visit 4 W+2	Visit 5 W+4	Visit 6 à 13 M3 to M24
Verification of the selection criteria	x					
Verification of the inclusion/exclusion criteria Pregnancy test (if applicable)	x					
Information/Informed consent	x					
Physical examination	x	x	x	x	x	x
ECG	x					
Dispensing of medication	x		x		x	x
Self-questionnaires on quality of life	x					x (**)
Randomisation			x			
Blood potassium	3/week	3/week	3/week	3/week	x	x
Verification of compliance		x	x	x	x	x
Dosage increase		x	x	x	x	x
Dosage adjustment (if necessary)				x	x	x
Concomitant treatments	x					x
SAEs		x	x	x	x	x

(**) only at V6, V9, V13, V17 and V21

1.3.6 Studied population

The studied population is patients with end-stage renal disease (ESRD) requiring haemodialysis (HD) - ESRD HD patients.

Inclusion criteria:

1. Adult men and women (INCLU1)
2. On haemodialysis for at least 45 days for ESRD regardless of aetiology including diabetes (INCLU4)
3. Weekly frequency of dialysis sessions of at least 3 per week (INCLU5)
4. Patient with at least one of the following comorbidities,

   cardiovascular abnormalities or CV risk factor: left ventricular hypertrophy defined as a left ventricular mass > 130 g/m^2 in men and 100 g/m^2 in women (echocardiography) (INCLU6) OR Cornell Index (RaVL + SV3)> 28 mm in man,> 20 mm in women (electrocardiogram) (INCLU7), OR left ventricular ejection fraction <40% (echocardiography) (INCLU12 if not missing else INCLU8); or QRS wide> 0.14 sec (INCLU9) OR Left branch block (electrocardiogram) (INCLU10) measured in the twelve months preceding the inclusion;

   Diabetes (INCLU13);

   History of CV disease: coronary artery disease (INCLU14), or Symptomatic lower limb peripheral artery disease (INCLU15), or Carotid or renal artery stenosis > 50% (INCLU16), or Stroke (INCLU17), or Hospitalisation for heart failure (INCLU18), or Atrial fibrillation (AF) (INCLU11), or Current oral anticoagulant therapy for AF

indication(INCLU20) , cardiac valve prosthesis (INCLU21) or CRP > 5 mg/l since the last 3 months in the absence of currently documented infectious or neoplastic disease(INCLU19)

5. Patient having given his or her free and informed written consent (INCLU2)
6. Patient affiliated with social security scheme (INCLU3)

Exclusion criteria:

1. History of hypersensitivity to spironolactone (EXCLU1)
2. Patients with galactose intolerance, Lapp lactase deficiency or glucose or galactose malabsorption syndrome (EXCLU1)
3. Hyperkalaemia> 5.5 mmol/l during the two weeks prior to inclusion, or history of unscheduled haemodialysis for hyperkalaemia in the last 6 months, or hospitalisation for hyperkalaemia in the last six months (EXCLU2)
4. Mandatory indication for a combination of ACE-I and sartan or renin inhibitor (each being authorised separately) (EXCLU3)
5. Concurrent therapy that cannot be stopped by another potassium-sparing diuretic, potassium supplementation, NSAIDs or Cox-2 inhibitors (EXCLU3)
6. Kidney transplantation scheduled within the year (EXCLU4)
7. Symptomatic interdialytic hypotension (EXCLU5)
8. Acute phase of systemic disease (EXCLU6)
9. Uncompensated hypothyroidism (EXCLU7),
10. Acute hyperthyroidism (EXCLU8)

Moderate abnormalities in thyroid function tests are very common in dialysis patients. Experience shows that the at-large interpretation of hormone assays or biomarkers is difficult. In order to confirm decompensation, extremely high (hypothyroidism) or truly collapsed (hyperthyroidism) TSH levels are needed, accompanied with highly disrupted T3 and T4 levels. Moreover, acute hyperthyroidism is accompanied by symptoms or complications.

11. Any prior or concomitant clinical condition compromising the inclusion, at the discretion of the investigator (EXCLU9)
12. Heart transplantation(EXCLU10)
13. Severe uncontrolled arrhythmia(EXCLU11)
14. Stroke within 3 months prior to inclusion(EXCLU12)
15. Acute coronary syndrome in the month preceding inclusion(EXCLU13)
16. Recent (1 month) or planned coronary revascularisation by angioplasty (EXCLU14)
17. Recent (3 months) or planned CV surgery, other than the vascular access for HD(EXCLU15)
18. Woman of childbearing age without effective contraceptive methods (i.e. in the absence of contraindication, use of an oestrogen-progestin or progestin contraceptive, contraception (oral, transdermal, or implant) or an intrauterine device or local contraception (condoms or spermicidal gels), or a history of tubal ligation, adnexectomy or hysterectomy) (EXCLU21)
19. Pregnancy, breastfeeding or planning a pregnancy within 2 years(EXCLU22)
20. Uncooperative patient or whose compliance to the dialysis treatment (frequency of sessions) or to the protocol is uncertain (including planned absence during the first two months of the study) (EXCLU16).
21. SBP> 200 mmHg and/or DBP> 110 mmHg(EXCLU17)

22. Inability to provide enlightened information to the subject (subject in emergency situation, subject with difficulties in comprehension, etc.) (EXCLU18)
23. Subject under judicial protection (EXCLU19)
24. Subject under guardianship or curatorship (EXCLU20)

1.3.7 Interim analysis

No formal efficacy interim analysis was planned.

Oversight Committee: three safety analyses were performed during the study period. These analyses were conducted after the obtaining and follow-up of at least one month of 1/4, 1/2 and 3/4 of the patients to be included. All relevant events and SAE were reported (no statistical test).

The Oversight Committee recommended the continuation of the study.

2 Analysis sets

Data of patients without informed consent in compliance with French law or patients who withdrew their consent to participate in the study and specifically requested that their data be removed from the database, will be removed from the analyses.

2.1 Run-in period population (run-in period)

All included patients entering the run-in period and taken at least one dose of spironolactone

2.2 Intent-to-treat population (ITT)

The intent-to-treat population is defined as all randomised patients irrespective of the received treatment, whether assessable or not).

The analyses will be performed as intent-to-treat, according to the treatment assigned by the randomisation scheme (unless specifically stated for some of the criteria).

2.3 Per-protocol population (PP)

The PP population includes all randomised patients who received the study treatment assigned by the randomisation scheme and who did not experience any major protocol deviation.

A list of patients to be excluded from the randomised patients to create the PP-efficacy population will be established and validated by the Steering Committee prior to database lock. A corresponding file will be prepared by the Coordinating centre, with the following items: Centre ID, Patient ID, reason for exclusion, and transferred with the final database.

The major protocol deviations considered are reported below:

- Patients who did not meet the inclusion or exclusion criteria
- Errors in treatment administration/allocation
- Spironolactone added on and reported during study visits
- Treatment withdrawn at randomisation visit (study treatment never administered)

2.4 Safety population

The Safety Population includes all randomised patients who received at least one dose of study drug. In case of violation of the randomisation scheme, patients will be classified according to the treatment they actually received.

2.5 Flow chart

The study flow chart is constructed according to the CONSORT recommendations (appendix 1 CONSORT 2010 Flow diagram and check list).

All patients included will be accounted for this study flow chart.

1. Total number of patients included

2. Number of included patients with informed consent (Patient's consent date not missing)

3. Number of included patients in the run-in period (run in attribution not missing)

4. Number of randomised patients (Patient's randomisation date not missing)

5. Number of included, run-in period, randomised patients for each centre

6. Number of randomised patients who completed the study, or discontinued after randomisation and main reason

7. Number of randomised patients at each follow-up visit and length of follow-up

The frequency and percent of subjects in each population (ITT, per-protocol, and safety), overall and by treatment groups, study withdrawals, subgroups, and major protocol violations will also be presented.

3 Analysis methods

3.1 General issues for statistical analyses

Statistical software

All statistical analyses will be performed using SAS® Software version 9.4 in a Windows environment, or R software version 3.6.3.

Missing data and outliers

All efforts will be made to collect outcome data including in patients withdrawn from the trial for whichever reasons and to minimise the amount of missing data. Unless specifically indicated, missing data will not be replaced. Outliers will be discussed as to whether to be kept or set as missing prior to database lock.

Stratification and centre effect

Unless otherwise specified, the treatment effect will be estimated on the primary and secondary outcomes after adjustment on the stratification variable.

Data transformation

Analysis of continuous variables may require transformation to normalise the distributions if the latter is justified to fulfil the hypotheses of the statistical methods to be used.

Derived and computed variables

Calculated delays since randomisation will be calculated as the time elapsed since the day of randomisation (day zero).

Delays will be converted in years or months by dividing the delays by 365.25 days or 30.4375 days respectively.

Duration=Delay+1 (days)

For the patient's date of birth, if no day is entered then it will all be replaced by 15.

Some derived and computed variables (such as delays) have been initially identified, and are described later in the document. It is expected that additional derived variables may be required. The SAP will not be amended for additional variables that are not related to the primary target or key secondary target variables. Any additional derived or computed variables will be identified and documented in the SAS programs that create analysis files.

Usual statistical presentations and tests

Description of continuous variables includes the mean, standard deviation, median, 1st and 3rd quartile, and range.

Description of categorical variables includes the frequency and percentage (based on non-missing values). Description of ordered variables includes the frequency, percentage and cumulative percentage.

Unless otherwise specified, between-group differences will be tested using the Wilcoxon rank-sum test for quantitative outcomes (or Student’s t-test in case of normal distribution), using Fisher’s exact test for binary outcomes, and the Mantel-Haenszel Chi-square test for ordinal outcomes.

Survival estimations will be performed using the Kaplan-Meier method [3].

A two-sided P value of less than 0.05 will be considered to indicate statistical significance. Two-sided Wald 95% confidence intervals will be used, except for median difference estimated using Hodges-Lehmann method.

Unless stated, no adjustment on p values for multiple tests will be made, thus the 95% confidence intervals should be interpreted descriptively and used as a measure of precision.

3.2 Descriptive analysis

3.2.1 Demographics and baseline characteristics

Patient characteristics at visit V1 and visit V3 (randomisation visit), will be described globally in the run-in population and globally and by treatment group in the ITT and PP populations, using usual descriptive statistics.

Following the CONSORT recommendations, no statistical tests will be performed to compare the studied groups (Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. CONSORT 2010 Explanation and Elaboration: Updated guidelines for reporting parallel group randomised trials. J Clin Epidemiol. 2010;2010(63):e1–37).

Demographic and baseline characteristics

Age

Sex

Current or past smoking

Diabetes

Dyslipidaemia

Hypertension

Waist circumference

Weight before and after a dialysis session

IMC

Heart rate before and after a dialysis session

Systolic and diastolic blood pressure in lying position before and after a dialysis session, first measurement and mean of second and third values.

Systolic and diastolic blood pressure in standing position before and after a dialysis session, first measurement and mean of second and third values.

History of cardiovascular disease

History of heart failure hospitalisation

EF <40 % at baseline

Left ventricular hypertrophy

History of atrial fibrillation

ECG characteristics AFib, QRS size, Cornell index, paced …

NB: Centralized ECG results are not available in the frozen database at the time of the SAP finalisation. These variables will be analysed later on.

Disease characteristics

First renal replacement treatment

Renal transplant

Date of first renal replacement treatment

Cause of ESRD:

- Arteriolar nephrosclerosis

- Glomerulonephritis or vascular nephritis
- Diabetes
- Tubulointerstitial nephropathy
- Hereditary or polycystic cause of ESRD
- Other cause of ESRD

Being on a waiting list for renal transplantation

Haemodialysis characteristics

Last measurement of residual diuresis in mL/24h (in the last 3 months)

Weekly frequency of dialysis sessions

Haemodialysis duration

Blood flow

Maximal ultrafiltration rate

Online haemodiafiltration

Potassium concentration in dialysis bath

Calcium concentration in dialysis bath

Type of vascular access

Potassium concentration

Laboratory characteristics

Blood glucose

Calcium level

Phosphorus level

Sodium level

Total cholesterol level

High-density lipoprotein (HDL) level

Triglyceride level

C-reactive protein (CRP) level

Albumin level

Haemoglobin level

Haematocrit

Haemoglobin A1c level in case of diabetes

PTH

Kt/V urea

25-OH vitamin D level

1,25-dihydroxy vitamin D level

Ferritin level

Medications

Concomitant treatments: ACE inhibitors, ARBs, potassium-sparing diuretic (potassium chelator), loop diuretic, potassium concentration in dialysis bath, or other

Other concomitant treatments at visit V1: spironolactone, statin, betablocker, antiplatelet, anticoagulant or others…

3.2.2 Follow-up data

For ITT and PP populations, follow-up variables will be described by treatment group using usual statistical tests (cf. paragraph 3.1).

Descriptive statistics for visits V2 and V3 to final visit

Weight before and after a dialysis session

Systolic blood pressure in lying position before and after a dialysis session, first measurement and mean of second and third values

Systolic blood pressure in standing position before and after a dialysis session, first measurement and mean of second and third values

Potassium concentration before a dialysis session

Concomitant treatments: ACE inhibitors, ARBs, potassium-sparing diuretic (potassium chelator), loop diuretic, potassium concentration in dialysis bath, or other

3.2.3 Administration of the study treatment

Run-in period

On the run-in period population, the duration of run-in treatment will be described overall according to usual descriptive statistics (cf. paragraph 3.1), considering the following definition:

Run-in treatment duration **=**Duration between first intake at visit V1 and last medication taken.

Study treatment period

Study treatment administration will be described on ITT and PP populations by treatment group according to usual descriptive statistics (cf. paragraph 3.1), considering the following definition:

Treatment total duration =Duration between intake at randomization and last medication taken

NB: The study drug dose was not collected in the eCRF at each visit, only adaptation of doses are available. These variables will be analysed later on.

The premature drug withdrawal, duration and reason will be also described on each population.

3.2.4 End of study

For each run-in period, ITT and PP populations, total follow-up length of study and reason for early termination will be described.

Completed the entire study

End of study date and reason

3.3 Primary efficacy analysis

Statistical analysis of the primary endpoint will primarily be based on the intent-to-treat population.

3.3.1 Primary efficacy endpoint

The primary endpoint is the time from randomisation to the onset of the first adjudicated expanded MACE event: non-fatal myocardial infarction (MI), acute coronary syndrome (ACS), hospitalisation for heart failure, non-fatal stroke, or cardiovascular death. Events were adjudicated and confirmed by an independent clinical event adjudication committee.

The full available follow-up time is the duration until all events are observed. Patients are censored at the date of renal transplantation. Patients that have shown no event and no renal transplant are censored at the date of the last available follow-up status (end of study or death, whichever occurred first), if any.

For analysis of time to first event, data will be expressed as two variables:

• A binary variable indicating whether any of the events included in the primary endpoint occurred, or the patient was censored.

• An integer variable for the number of days from randomisation to the first occurrence of an event (start date of the event – randomisation date + 1), or for event-free patients, from randomisation to censoring (censoring date – randomisation date + 1).

censored	date
0 (event)	Start date of the event is the first between : - Date of cardiovascular death - Date of cardiovascular event
1 (no event)	Censoring date is the first, following this order, between: - Date of renal transplantation - Date of death if not cardiovascular cause - Date of end of study alive

NB: cf. Appendix 2 eCRF data to construct the primary endpoint (to independent reprogramming)

In the case where several events comprising the primary outcome occur on the same day, CV death is prioritised over non-fatal CV event for description purposes.

3.3.2 Formal analysis

Main analysis

Experimental treatment will be compared using the statistical framework of proportional hazards survival model adjusted on treatment group (spironolactone versus placebo) and stratified or adjusted by centre (randomisation stratification variable). The outcome is described in Section 3.3.1. The proportionality assumption will be assessed by analysing Schoenfeld residuals and examining log-log survival plots. The Efron method for ties and p-value based on the Wald statistic will be used. The event rates, p-value, HR, and 95% confidence interval will be reported.

In case of evidence of non-proportionality, a cautious interpretation of the model will be encouraged, and a weighted (Kaplan-Meier or Cox) or a parametric model event rate estimate will be emphasised.

Kaplan-Meier estimates of the cumulative proportion of patients with event will be calculated and plotted, for the composite endpoint and for each event types of the primary endpoint. The plot will include the number of subjects at risk for each treatment group over time.

Depending on the heterogeneity of the center effect and conditional on a sufficient number of patients by centre, a frailty proportional hazard regression [4, 5, 6] could be fitted, with the centre as random effect and treatment group as fixed effect. Random effect is used to account for correlation between observations within each centre and assumes a single hazard baseline function per centre.

If the number of randomised patients per centre is too low, they will be clustered according to their similarity in ARDS patients, or the number of included patients (for example “Limoges” vs. “others”) in 2 or more groups in order to sustain the hypothesis .

If no heterogeneity is observed, an unadjusted on centre Cox proportional hazard regression will be fitted.

Component of the primary endpoint:

The contribution of each component of the primary endpoint to the overall treatment effect will be examined. The first event of each given type of event will be included, irrespective of any preceding non-fatal event of a different type. Consequently, the sum of the number of patients with events in the component analysis will be larger than the number of patients with composite events. Methods similar to those described for the primary analysis will be used to separately analyse the time from randomisation to the first occurrence of each component of the primary composite endpoint.

3.3.3 Multivariate analysis

An adjusted survival analysis will be performed with treatment group and covariates, listed below:

Characteristic	Categories
Age (years)	<= 75, >75 or <=median, >median
Preexisting diabetes at baseline	Yes, No
History of ASCVD	Yes, No

3.3.4 Subgroup analysis

Conditional to the number of events in each subgroups, the primary composite endpoint will be analysed for the characteristics listed in paragraph 3.3.3 Multivariate analysis

A test of interaction between randomised treatment group and the subgroup variable will be performed in each survival model, including as covariates: treatment group, the relevant subgroup variable and the interaction between treatment and the subgroup variable. In addition to the number and percent of patients with event, the event rate estimate, HR with 95% confidence interval for each subgroup and the interaction will be presented. HRs with confidence intervals will be presented in a forest plot, also including the event rate.

Other categories for subgroup analyses of the primary endpoint

Characteristic	Categories
IMC (kg/m²)	<= ,>30 or <23 ,23-30 >30 or according to quantiles
history of HF hospitalisation	Yes, No
EF < 40%	Yes, No
Serum potassium at baseline	<= 4.5, >4.5 or <=median, >median
Use of potassium binder at baseline	Yes, No
Use of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blocker (ARB) at baseline	Yes, No
Systolic blood pressure at baseline	≤ median, > median
Dialysis vintage	≤ median, > median
Haemodiafiltration	Yes, No

3.3.5 Sensitivity analysis

The following sensitivity analyses will be performed on the primary composite endpoint:

- **Analysis using the PP analysis set**

- **Informative censoring**

In the primary survival analysis, renal transplantation could prevent the observation of the primary endpoint, and therefore is an informative censoring.

Renal transplant patient characteristics will be described. In addition, time to renal transplantation will be analysed to identify if this censoring process changes the "at risk" population in the primary survival model. Hence a competing risk framework could be used to verify the impact on the model estimations.

3.3.6 Exploratory analysis

- **Impact of the COVID-19 period on primary composite endpoint and CV death survival plots according to the date of onset of the epidemic period, according to international guidance's:**

  Anker SD, Butler J, Khan MS, Abraham WT, Bauersachs J, Bocchi E, et al. Conducting clinical trials in heart failure during (and after) the COVID-19 pandemic: an Expert Consensus Position Paper from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur Heart J 2020; 41: 2109–2117.

  European Medicines Agency. Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic. April 2, 2021 (version 4). https://ec. europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_ covid19_en.pdf (22 April 2021).

  US Food and Drug Administration. FDA guidance of conduct of clinical trials of med- ical products during COVID-19 public health emergency. March 2020 (Updated January 27, 2021). https://www.fda.gov/media/136238/download (17 February 2021).

A complementary analysis of exposure to COVID-19 infection could be performed adjusting the primary endpoint model on a time-dependent covariate "exposed/non-exposed COVID-19 patients" with 01/01/2020 as first exposed time. An effect of interaction between randomised treatment group and the time dependant covariate will be assess in the model.

- **Investigator-reported (non-adjudicated) primary endpoint events**

Expanded MACE events as reported by the investigators, independent from the critical event committee adjudication process

3.4 Secondary efficacy analysis

Statistical analysis of the secondary endpoints will be performed on the Intent-to-treat population. Secondarily, the same analyses will be repeated on the per-protocol population.

3.4.1 Secondary endpoint part 1

To handle the multiple testing, outcomes will be analyzed using a hierarchical testing procedure until the p-value equals or exceeds 0.05, the primary outcome being the most important outcome, followed by the secondary outcomes ranked according to the importance order shown in below. The secondary objective will be considered by comparing the effects of spironolactone to placebo on: Composite of (1) death from any cause and (2) time to CV non-fatal event (hospitalisation for heart failure or non-fatal MI or acute coronary syndrome or non-fatal stroke) both at 2 years.

A composite endpoint, Finkelstein-Schoenfeld z score [8], is based on a combination of 1) all-cause mortality and 2) time to CV non-fatal events, both at 2 years, assuming a hierarchy of the two endpoints. Each patient *i* is compared to each patient *j* of the clinical trial in a pairwise manner and assigned a score, u_{ij}, of -1, 1 or 0, depending on whether the outcome is unfavourable, favourable or indeterminate in the hierarchy of outcomes. Thus, if patient *i* died before patient *j*, the score is -1; if patient *j* died before *i*, the score is 1. If it cannot be determined which patient died first (e.g., because of equality or censoring), then the second outcome (time to CV event) is compared and assigned a value of 1 or -1 depending on whether patient *i* has a better outcome or not. When it cannot be determined whether a patient has a more favourable outcome than the other (equality or censor at 2 years), then the score is assigned a value of 0.

The Finkelstein-Schoenfeld z score is based on the sum of patient scores in the experimental arm, and this statistical test assesses significant differences on the composite endpoints.

« Unmatched WinRatio » [9] estimates the effect of experimental treatment on the composite endpoints, death from any cause and time to CV event (excluding death) both at 2 years. For pairs of patients, each patient in the experimental arm is compared to each of the other patients in the standard arm. The WinRatio is the ratio of the number of winners (pairs in which the patient in the experimental treatment has a better outcome and the number of losers (pairs where the patient in the experimental treatment has a worse outcome. The 95% confidence intervals for the win ratio can be computed using Bootstrap (SAS macros are available from duolao.wang@lshtm.ac.uk, WinRatiofinal.sas and WinratioFinal_bootstrapFinal.sas [Finkelstein and al., Pocock and al.] or a R package is available).

Conditional on a sufficient number of patients in each centre (randomisation stratification variable), a stratified win ratio statistic could be calculated [10].

A sensitivity analysis of the winratio will include events occurring after 2 years of follow-up.

Components of the winratio:

Each component of this composite endpoint to the overall treatment effect will be examined. Methods similar to those described for the primary analysis will be used to analyse time to all-cause death and time to CV event.

In addition, an analysis similar to the primary analysis will assess and illustrate the impact of the COVID-19 period on the all-cause death survival plot according to the date of onset of the epidemic period.

A sensitivity analysis of time to all cause death endpoint will be performed with no censoring at the renal transplantation.

Additional secondary endpoints will be considered for hypothesis raising

3.4.2 Secondary endpoint part 2-a

Analyses similar to the primary composite endpoint analysis will be performed to analyse the time from randomisation to the first occurrence of death from a non-CV cause.

3.4.3 Secondary endpoint part 2-b

The cumulative rate of multiple non-fatal events comprising the primary outcome events: hospitalisation for heart failure or non-fatal MI or acute coronary syndrome or non-fatal stroke and occurrence of death i) from any cause, ii) from a CV cause, iii) from a non-CV cause.

The primary endpoint considers five distinct events; however, in each patient, multiple events may occur over time. Thus, the effect of treatment on the cumulative rate of events may be estimated taking into account the recurrence of events (and not only the first event). The number of events per patient will be described and compared using usual quantitative statistics.

Conditional to the cumulated number of adjudicated MACE events per patient, a survival analysis, i.e. the independent increment model of Anderson and Gill [5, 7], is an approach to analyse recurrent events. The model of Anderson and Gill is an extended Cox model that is a regression of the intensity of a recurrent event. The effect of treatment on the cumulative rate of events can be estimated with its statistical significance (Wald test). This analysis can be performed with adjustment on the "centre" variable and other variables.

3.4.4 Secondary endpoint part 2-c

Survival time without a major cardiovascular event: non-fatal MI, acute coronary syndrome, hospitalization for heart failure, non-fatal stroke, or cardiac arrest resuscitation (Diagnostic or MedDRA codage, EI_date (Table EI)) will be analysed using a similar methodology to that of the main analysis of the primary composite endpoint. .

3.4.5 Secondary endpoint part 2-d, part 2-e and part 2-g

- Incidence of procedures related to a stenosis or thrombosis of the vascular access for haemodialysis (Diagnostic or MedDRA codage, EI_date (Table EI))
- Incidence of coronary or peripheral revascularisation (including lower limb amputations) (Diagnostic or MedDRA codage, EI_date (Table EI)
- incidence of complete atrial fibrillation arrhythmia (Diagnostic or MedDRA codage, EI_date (Table EI))

The incidence and number of each procedure for stenosis or thrombosis at the site of vascular access for dialysis and the incidence of any coronary or peripheral revascularisation (among lower limb amputations) will be described using the "usual statistics".

3.4.6 Secondary endpoint part 2-f

Blood pressure (pre- and post-dialysis) and its inter-visit variability

Referring to the publication by Rossignol and al. [11], a coefficient of variation for values at each visit time will be calculated and compared between treatment groups (spironolactone vs. placebo). The parameter will be described and compared using the usual statistics.

An alternative method could be performed, conditioned to model hypothesis, to evaluate treatment group effect on blood pressure mean values and variabilities using a Mixed Model for Repeated Measures (MMRM).

3.4.7 Secondary endpoint and part 2-h

- incidence of hyperkalaemia > 6 mmol/L (Diagnostic or MedDRA codage, EI_date (Table EI) with DIAGNOSTIC='7' (hyperkaliemie >6 mmol/l) and EI_GRAVE=1 or LLT containing ('HYPERKALEAMIA' and EI_GRAVE=1), as
    i. reported anytime and with any method during follow up (Time to first and recurrent)
    ii. reported at per protocol scheduled visits (Time to first and recurrent)

The incidence and number of each event will be described and compared using the usual statistics.

Sensitive analysis of serum potassium could be considered:

- incidence of hyperkalaemia ≥ 5.5 mmol/L, as
    i. reported anytime and with any method during follow up (Time to first and recurrent)
    ii. reported at per protocol scheduled visits (Time to first and recurrent)
- Serial changes and variability of serum potassium at scheduled per-protocol visits over time (visit V1 to visit V5)

  For the analysis of longitudinal data for serum potassium values, summary parameters (auc, means, etc.) could be estimated and compared between treatment groups. A mixed model for repeated measures (MMRM) could be performed to estimate marginal means and variabilities.
- incidence of hypokalaemia at <4 mmol/L and <3.5 mmol/L, as
    i. reported anytime and with any method during follow up (Time to first and recurrent)
    ii. reported at per protocol scheduled visits (Time to first and recurrent)

3.4.8 Secondary endpoint part 2-i

Quality of life analysis will be described in the dedicated QoL SAP document (Nancy CIC-EC team).

3.4.9 Secondary endpoints part 3

Establishment of a biological collection for future biomarker studies (serum bank and DNA library).

A post-study will assess the rate and the time-to-event (mortality and cardiovascular morbidity) at 3, 5, and 10 years, using a French national epidemiological registry (No data for now).

A health economics ancillary study will complete this project. The statistical analysis of the health economics parameters will be performed by the Centre d'Investigation Clinique - Epidémiologie Clinique, Nancy, France.

3.5 Safety analysis

Adverse events (AE) were coded by the central safety desk using the MedDRA dictionary with their Preferred Term (PT), High Level Term (HLT) and System Organ Class (SOC) term.

Safety endpoints will be assessed firstly on the run-in period population.
All AE emerging between first run-in intake date of treatment and end date of the run-in period will be described overall by SOC, and PT (or HLT).

Secondly, safety endpoints from randomization will be assessed on the safety population, overall and by treatment group, as following detailed:

3.5.1 General Safety analysis

All AE and serious adverse events (SAE) emerging after the first study drug intake (Diagnostic or MedDRA codage, EI_date (Table EI) will be described overall and by treatment group by SOC, and PT (or HLT).
Number of patients (%) with at least one event
Number of events
Number of events per patient
Number of patients (%) with at least one events and number of events by SOC / HLT (or PT)
Number of patients (%) with at least one events related to treatment and number of events by SOC / HLT (or PT)

Deaths**:** (PATIENT_DCD, DATE_DC, RESU_ADJU_DC, COM_DC (tables DECES and EVENEMENTS_INTERET) or Diagnostic or MedDRA codage, EI_date (Table EI))
Number of patients (%) with a fatal events

No statistical tests will be performed.

3.5.2 Adverse event of special interest

All AE of special interest emerging after the first study drug intake (Diagnostic or MedDRA codage, EI_date (Table EI) will be described overall and by treatment group.
Events or effects related to the active drug:

- Gynecomastia
- Impotency (Rare)
- Menstrual disorders (Rare)
- Digestive intolerance (Rare)
- Skin rash (Rare)
- Drowsiness (Rare)
- Cramps

Events related to the initial disease (ESRD + CV risk):

- Nonfatal MI and acute coronary syndrome,
- Heart failure
- Nonfatal stroke
- Revascularisation (coronary, carotid, lower limbs, vascular access)
- Complete arrhythmia due to atrial fibrillation
- Kidney transplant
- Hospitalisation for hyperkalaemia
- Infection
- Hyperkalaemia

No statistical tests will be performed.

4 Quality assurance

Data entry

Data entry and data quality controls will be described in the Data management plan document.

Statistical analysis

The construction and analysis of the primary endpoint will be independently performed from the raw data by a second biostatistician, and compared with the results of the trial statistician.

5 Bibliographic references

1. Cox DR et Oakes D. Analysis of Survival Data. 1984 ; London ; Chapman & Hall.

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4. Rondeau V and Commenges D. Modélisation de la fragilité en survie. Journal de la Société Française de Statistique 2002;,143: 103-119.

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6. Hougaard P. Frailty models for survival data, Lifetime Data Analysis 1995; 1:255-273.

7. Andersen PK and Gill RD. Cox's regression model for counting processes: A large sample study. Annals of Statistics 1982; 10:1100–1120.

8. Finkelstein DM, Schoenfeld DA. Combining mortality and longitudinal measures in clinical trials. Stat Med. 1999;18:1341-1354.

9. Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. Eur Heart J. 2012;33(2):176-182.

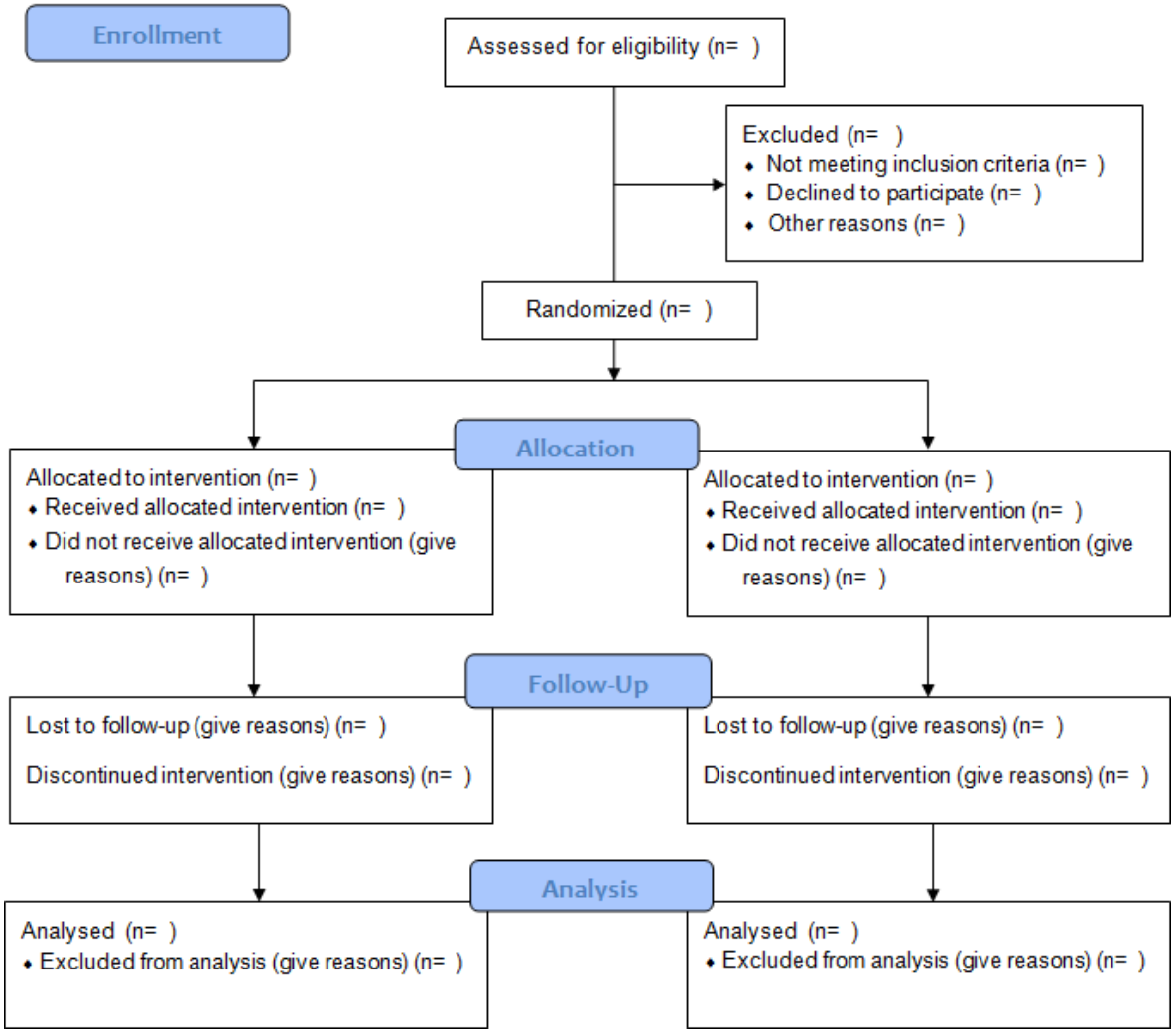
10. Dong G, Hoaglin DC, Huang B, et al. The stratified win statistics (win ratio, win odds, and net benefit). Pharmaceutical Statistics. 2023;1-9. doi:10.1002/pst.2293

11.Rossignol and al. Visit-to-Visit Blood Pressure Variability Is a Strong Predictor of Cardiovascular Events in Hemodialysis Insights From FOSIDIAL, Hypertension. 2012;60:339-346.)

Appendix 1 Consort Flow Diagram and Checklist

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item
Title and abstract		
	1a	Identification as a randomised trial in the title
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONS
Introduction		
Background and objectives	2a	Scientific background and explanation of rationale
	2b	Specific objectives or hypotheses
Methods		
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons
Participants	4a	Eligibility criteria for participants
	4b	Settings and locations where the data were collected
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when t
	6b	Any changes to trial outcomes after the trial commenced, with reasons
Sample size	7a	How sample size was determined
	7b	When applicable, explanation of any interim analyses and stopping guidelines
Randomisation:		
Sequence generation	8a	Method used to generate the random allocation sequence
	8b	Type of randomisation; details of any restriction (such as blocking and block size)
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered contai to conceal the sequence until interventions were assigned
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participa
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, how
	11b	If relevant, description of the similarity of interventions
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses
Results		
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatm primary outcome
	13b	For each group, losses and exclusions after randomisation, together with reasons
Recruitment	14a	Dates defining the periods of recruitment and follow-up
	14b	Why the trial ended or was stopped
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the an groups
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size confidence interval)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended

Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, d exploratory
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms
Discussion		
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyse
Generalisability	21	Generalisability (external validity, applicability) of the trial findings
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evid
Other information		
Registration	23	Registration number and name of trial registry
Protocol	24	Where the full trial protocol can be accessed, if available
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Appendix 2 eCRF data to construct the primary endpoint (to independent reprogramming)

The items entering to construct the primary endpoint are given in the tables below:

Cardiovascular death

Variable name	eCRF Table	Variable label	Visit
SUBJID	BASE_STAT	Subject Identifier for the Study	V3
DATE_RANDOMISATION (constructed) = DATE_VISITED1	BASE_STAT	Randomisation date	V3
CODE_TRAITEMENT	BASE_STAT	Code de traitement	V3
DATE_DECESD1	DECES	date décès	
DC_RESU	DECES	Résultat de l'adjudication	
CV_DEATH (constructed)		CV death (binary)	

CV_DEATH = 1 (yes) when DATE_DECESD1 is not missing and DC_RESU in (“1”,”2”)

Cardiovascular events (excluding death)

Variable name	eCRF Table	Variable label	Visit
INT_DEBUTD1	EVENEMENTS_INTERET	date de début	
INT_RESU_ADJU	EVENEMENTS_INTERET	Résultat de l'adjudication	
CV_EVENT (constructed)		CV event (binary)	

CV_EVENT = 1 (yes) when INT_DEBUTD1 is not missing and INT_RESU_ADJU in ("1","3","5","7")

First cardiovascular event (before renal transplant)

Variable name	eCRF Table	Variable label	Visit
EI_DEBUTD1	EI	date de début	
EI_DIAG	EI	Diagnostic	
EI_PRECIS	EI	Diagnostic précision	
DATE_EVENT (constructed)		Date of CV event	

Assessment of adverse events with (EI_DIAG='16') or (DIAGNOSTIC (EI_PRECIS) containing (’RENALE’ and ’TRANSPLANTATION’) or (’RENALE’ and ’GREFFE’)) (table EI) to identify EI_DEBUTD1 for a renal transplant or FIN_RAISON=’ Transplantation rénale du patient’ (table Arret_ttt_fin_etude) .

If no renal transplantation before an event, DATE_EVENT = minimum date between DATE_DECESD1 when CV_DEATH=1 and INT_DEBUTD1 when CV_EVENT=1

First cardiovascular event (up to maximum follow-up to include all first events)

Variable name	eCRF Table	Variable label	Visit
EI_DEBUTD1	EI	date de début de la greffe rénale	
FIN_DATED1	Arret_ttt_fin_etude	Date de fin d'étude	
DATE_DECESD1	DECES	date de décès	
DATE_DDN (constructed)		Last censoring date	

DATE_EVENT (constructed)	First event date
EVENT (constructed)	1= first event or 0= no event at last date (binary) (primary endpoint)
DELSUIV (constructed)	Duration (months) between randomisation and first event or censoring (primary endpoint)

DATE_DDN = EI_DEBUTD1 if renal transplant,

if no renal transplant, DATE_DDN = FIN_DATED1 when FIN_RAISON^='6' (alive)

DATE_DDN = DATE_DECESD1 when FIN_RAISON='6' (death) and DC_RESU not in ("1","2") (cause of death not cardiovascular)

For each subject,

- if an event occurred [i.e. DATE_EVENT is not missing] DELSUIV = (DATE_EVENT – DATE_RANDOMISATION + 1)/30.4375 (months) and EVENT = 1
- if no event occurred DELSUIV = (DATE_DDN – DATE_RANDOMISATION + 1)/30.4375 (months) and EVENT=0

Statistical Analysis Plan

ALCHEMIST

ALdosterone antagonist Chronic HEModialysis Interventional Survival Trial

(Quality of Life Analysis)

V08 du 05/10/2023

Project initiators: Pr Patrick ROSSIGNOL et Pr Luc FRIMAT (CHRU de Nancy)

Project manager: Mme Angélique TENAILLEAU (CHRU de Brest)

Methodologist: Pr Francis GUILLEMIN (CIC 1433 Epidémiologie Clinique
CHRU Nancy, Inserm, Université de Lorraine)

Statistician: Willy NGUEYON SIME (CIC 1433 Epidémiologie Clinique
CHRU Nancy, Inserm, Université de Lorraine)

Sommary

Signature page

Trial biostatistician

Name: Date:

Willy NGUEYON SIME October, 5rd 2023

Epidemiologist

Name: Date:

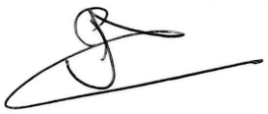
Pr Francis GUILLEMIN October, 5rd 2023

Approved by:

Coordinating Investigator

Name: Date:

Pr Patrick ROSSIGNOL October, 5rd 2023



1. Context

Chronic kidney disease (CKD) is a public health priority. The latest European data show an incidence of end-stage renal disease (ESRD) requiring renal replacement therapy of 118 per million inhabitants/year, a prevalence of 630 per million. The unadjusted mortality rate is 29% at 2 years and 52% at 5 years. ESRD is associated with increased cardiovascular (CV) morbidity and mortality (2 to 10 times that of a population with normal renal function). Heart disease is the leading cause of mortality in patients on hemodialysis (HD) (42% of total mortality). Despite these alarming observations, this syndrome remains the poor relation of CV prevention. Very few treatments are evidence-based and CKD patients on HD are usually excluded from CV prevention trials. Aside from two positive studies among ESRD HD patients with heart failure and severely impaired left ventricular ejection fraction (stages III-IV) using renin angiotensin aldosterone system (RAAS) blockers (beta-blocker carvedilol, or a combination of angiotensin converting enzyme inhibitor (ACE-I) with an angiotensin II receptor antagonist (ARA-II) telmisartan), two morbidity-mortality studies developed by the CIC-P Nancy, the designer of the present project, and specifically including ESRD HD patients, have showed on the one hand that a statin had no effect and, on the other, that an ACE-I had a positive effect (undersized study, generating a trend of efficacy). Another study conducted in HD diabetics showed that another statin had no effect. These limited and inconclusive experiences make further studies by the pharmaceutical industry unlikely in the coming years. In order to avoid that HD patients, often excluded from CV morbidity-mortality trials, remain without evidence-based therapeutic resources and continue to present unacceptable CV morbidity and mortality rates, institutionally-sponsored trials are needed. Our group has significant experience in morbidity-mortality trials in HD.

Clinical and experimental data suggest that RAAS blockade with ACE-I or ARA-II can limit atherosclerosis and CV morbidity and mortality, independently of blood pressure reduction, at least in subjects at high cardiovascular risk without severe renal impairment.

In none dialysed patients with heart failure, three international controlled trials showed a reduction in cardiovascular morbidity and mortality induced by aldosterone antagonists (spironolactone and eplerenone). Our group participated in the design, conducting and publication of these three studies. The beneficial effects of aldosterone antagonists involve cardiovascular remodelling, including collagen synthesis, as well as effects on endothelial and immune functions. A recent randomised controlled trial conducted in early-stage CKD showed that adding spironolactone to ACE-I or sartans reduces left ventricular mass and arterial stiffness, both of which are independent predictors of cardiovascular events in patients with ESRD. Most clinicians are reluctant to use aldosterone antagonists because of the risk of hyperkalaemia. However, recent studies have demonstrated the safety of spironolactone in anuric ESRD HD patients.

The primary objective is to determine the effects of Spironolactone versus Placebo on a combined endpoint of nonfatal myocardial infarction (MI) and acute coronary syndrome, hospitalization for heart failure, nonfatal stroke, or CV death.

The secondary objective, addressed by the present statistical analysis plan, is to estimate the effect of the treatment group (Spironolactone vs. Placebo) on the Quality of Life (SF-36; KD-QOL and Minnesota) of these patients with the dual pathology: CKD on hemodialysis and established cardiovascular pathology.

Data source(s):

- Data from the ALCHEMIST (ALdosterone antagonist Chronic HEModialysis Interventional Survival Trial) cohort.

2. Analysis objectives

The objective of the analysis is to estimate the effect of treatment group (Spironolactone vs. Placebo) on Quality of Life (QoL) measured by the SF-36 (generic questionnaire), the KD-QOL (kidney failure specific questionnaire) and the Minnesota Heart Failure (heart failure specific questionnaire) at various times during the trial (baseline, 3 months, 1 year, 2 years, 3 years and 4 years).

The analysis will be blinded to the treatment group attributed by randomization.

3. Analysis sample

A total of 750 randomized patients (375 per group) followed for an average of 4 years.

The analysis will be conducted on a intention-to-treat (ITT) and per-protocol (PP) basis, according to the populations defined in the statistical analysis plan of the primary objective (ITT and PP).

4. Study variables

a. Outcome

The outcome was each dimension of quality of life (Sf-36, KD-QOL and Minnesota). There is no unique score for each questionnaire.

For the method of calculating each quality-of-life dimension (Sf-36, KD-QOL and Minnesota), please refer to Appendix 1 (p. 12). The 2 components of the SF36 are each a weighted linear combination of the 8 dimensions of the SF36, with a different and specific weight for each Component.

- **SF-36** :
  - Physical Functioning [QT]
  - Role-Physical [QT]
  - Bodily Pain [QT]
  - Mental Health [QT]
  - Role-Emotional [QT]
  - Social Functioning [QT]
  - Vitality [QT]
  - General Health [QT]
  - Physical Component Summary [QT]
  - Mental Component Summary [QT]
- **KD-QOL** :
  - Burden of kidney disease [QT]

        - Symptoms/Problems [QT]
        - Effects of kidney disease on daily life [QT]
- **Minnesota** :
    - Physical [QT]
    - Mental [QT]
    - Social [QT]
    - Incapacity [QT]

- **Interest factor**
    - Treatment group (Spironolactone vs Placebo) (blind coded variable) [QL]

- **Confounding factors**
    - Age [QT]
    - Sex [QL]
    - Smoking [QL]
    - BMI [QT]
    - Center [QL]
    - Pre-existing CV disease [QL]
    - Pre-existing diabetes at baseline [QL]

- **Event variables**
    - Date of baseline
    - Date of birth
    - Follow-up time
    - Date of death
    - Date of last follow-up
    - Date of non-fatal event:
        - Hospitalization for heart failure
        - Non-fatal myocardial infarction (MI)
        - Acute coronary syndrome
        - Non-fatal stroke

- **Variables to be constructed**
    - BMI = weight/size²
    - Center to be grouped in the same way as for the principal analysis

Stratification and center effect

Unless otherwise indicated, the effect of treatment group will be estimated on results after adjustment for the stratification variable (center).

Missing data

Missing QOL data occur when no data values are missing for a variable for a given observation. We will describe missing QoL data (SF-36, KD-QOL and Minnesota) by item, by dimension (following the

imputation rules indicated by the developers of each questionnaire where applicable), by subject and by measurement time at inclusion, 3 months, 1 year, 2 years, 3 years and 4 years.

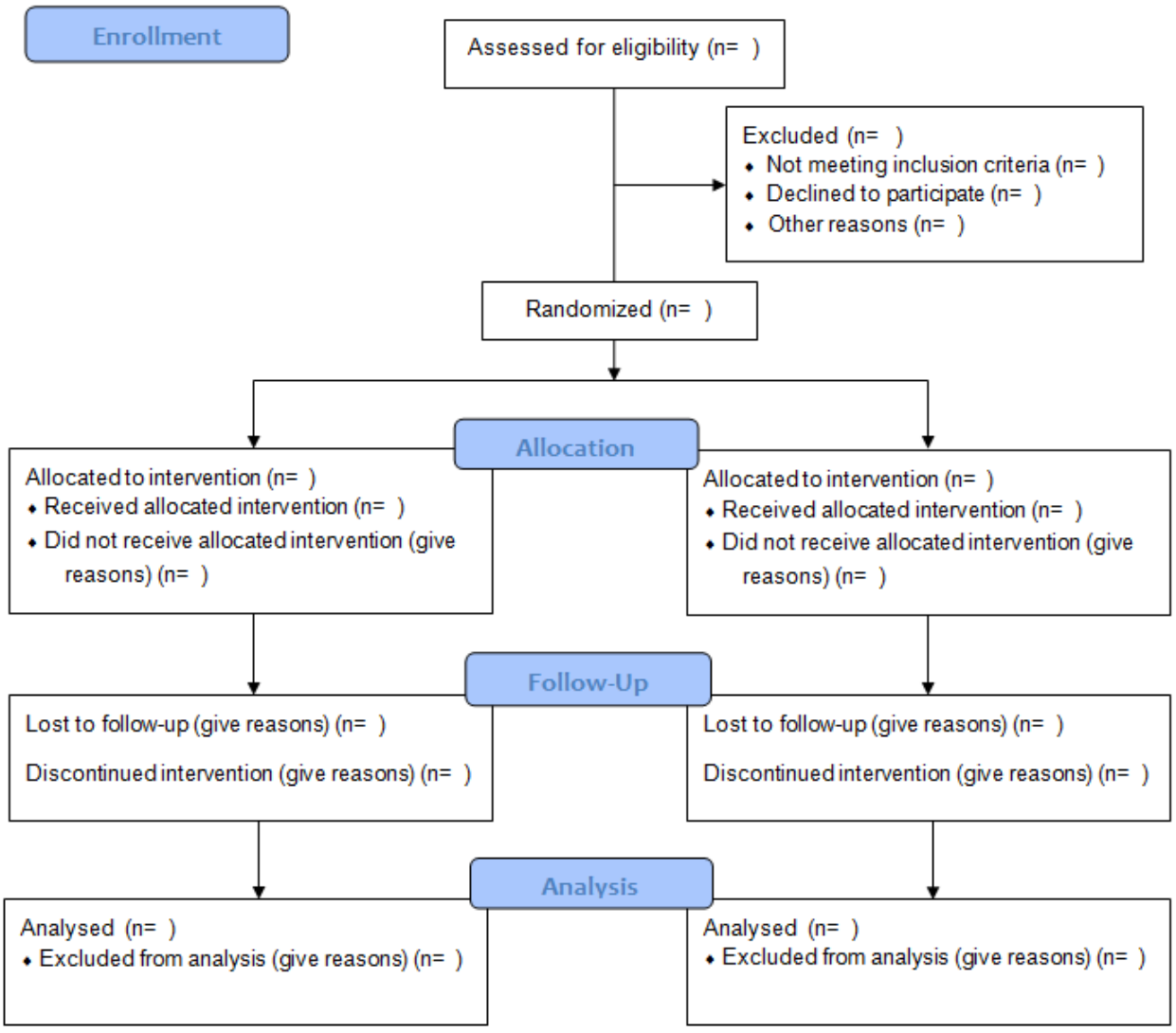
Missing data (missing questionnaires) may also occur in the event of death or discontinuation of subject follow-up. They will be documented according to the date of death or the date of last follow-up.

5. Statistical analysis

a. Flow Chart

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram



b. Descriptive analysis

Observed modalities of qualitative variables will be described by:

- **Numbers and percentages (%)**

Note: The number of missing data will also be presented.

Descriptive statistics for quantitative variables will be described by:

- **Number, Mean ± SD [95% CI], Median (Q1 - Q3) and Min - Max.**

Note: The number of missing data will also be presented.

Data to be described at inclusion and at each time point when available will be:

- **Quality of Life**
  - ✓ **SF-36** :
    - Physical Functioning [QT]
    - Role-Physical [QT]
    - Bodily Pain [QT]
    - Mental Health [QT]
    - Role-Emotional [QT]
    - Social Functioning [QT]
    - Vitality [QT]
    - General Health [QT]
    - Physical Component Summary [QT]
    - Mental Component Summary [QT]
  - ✓ **KD-QOL** :
    - Burden of kidney disease [QT]
    - Symptoms/Problems [QT]
    - Effects of kidney disease on daily life [QT]
  - ✓ **Minnesota** :
    - Physical [QT]
    - Mental [QT]
    - Social [QT]
    - Incapacity [QT]
  - ✓ **Interest factor**
    - Treatment group (Spironolactone vs Placebo) (blind coded variable) [QL]
  - ✓ **Confounding factors**
    - Age [QT]
    - Sex [QL]
    - Smoking [QL]
    - BMI [QT]
    - Center [QL]
    - Pre-existing CV disease [QL]

- Pre-existing diabetes at baseline [QL]

✓ **Event variables**
- Date of baseline
- Date of birth
- Follow-up time
- Date of CV death
- Date of last follow-up
- Date of non-fatal event:
  - Hospitalization for heart failure
  - Non-fatal myocardial infarction (MI)
  - Acute coronary syndrome
  - Non-fatal stroke

Repeated data
Repeated data will be described at each time point for all subjects and by treatment group.

A longitudinal description will then be carried out to give the numbers and values of variables for subjects with complete data at all times, and then at the various combinations of incomplete times.

c. Comparative analysis

A comparative analysis of Quality of Life dimensions (SF-36, KD-QOL and Minnesota) will be performed according to treatment group (Spironolactone vs. Placebo) at inclusion, 3 months, 1 year, 2 years, 3 years and 4 years.

Differences between treatment groups at baseline, 3 months, 1 year, 2 years, 3 years and 4 years will be tested using the Wilcoxon rank test for quantitative results (or Student's t-test in case of normal distribution).
A difference of 5 points (on a scale of 0 to 100) between treatment groups will be considered clinically significant for the interpretation of results (SF36 Health survey: Interpretation and guide, 1993).

The effect size, calculated as the mean difference between groups divided by its variance, will be assessed by the Cohen's D coefficient, and interpreted according to Cohen’s recommendations.

The evolution curve of the score of each dimension of quality of life and their 95% confidence intervals according to treatment group at inclusion, 3 months, 1 year, 2 years, 3 years and 4 years will be represented using the SF-36 norms available in the French population by age and sex, and the deviations from the French mean and by treatment group will be shown. We will perform the test to the theoretical mean for each dimension and the 2 components.

d. Subgroup analysis

Subgroup analyses of each quality-of-life dimension (SF-36, KD-QOL and Minnesota) will be performed for the characteristics listed below:

Characteristic	Categories
Age (years)	≤ 75, >75 or <=median, >median
Pre-existing diabetes at baseline	Yes, No
History of ASCVD	Yes, No
IMC (kg/m²)	≤30, >30 or <23 ,23-30, >30 or according to quantiles
History of HF hospitalisation	Yes, No
EF < 40%	Yes, No
Serum potassium at baseline	≤ 4.5, >4.5 or <=median, >median
Use of potassium binder at baseline	Yes, No
Use of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blocker (ARB) at baseline	Yes, No
Systolic blood pressure	≤ median, > median
Dialysis vintage	≤ median, > median
Haemodiafiltration	Yes, No

6. Principal analysis

The objective of the analysis is to estimate the effect of treatment group (Spironolactone vs. Placebo) on Quality of Life (SF-36, KD-QOL and Minnesota) measured at baseline, 3 months, 1 year, 2 years, 3 years and 4 years.

This leads us to take into account data repetition. We are in a case of analysis with repeated measurement (intra-subject correlation) and this leads us to use the **linear mixed model.**

A. Bivariate & Multivariate analysis

1. List of variables

➔ **Variables to be explained:**

- ✓ **SF-36** :
  - Physical Functioning [QT]
  - Role-Physical [QT]
  - Bodily Pain [QT]
  - Mental Health [QT]

- Role-Emotional [QT]
- Social Functioning [QT]
- Vitality [QT]
- General Health [QT]
- Physical Component Summary [QT]
- Mental Component Summary [QT]

✓ **KD-QOL** :

- Burden of kidney disease [QT]
- Symptoms/Problems [QT]
- Effects of kidney disease on daily life [QT]

✓ **Minnesota** :

- Physical [QT]
- Mental [QT]
- Social [QT]
- Incapacity [QT]

➔ **Explanatory variables**:

✓ **Interest factor**

- Treatment group (Spironolactone vs Placebo) (blind coded variable) [QL]

✓ **Confounding factors**

- Age [QT]
- Sex [QL]
- Smoking [QL]
- BMI [QT]
- Center [QL]
- Pre-existing CV disease [QL]
- Pre-existing diabetes at baseline [QL]

✓ **Event variables**

- Date of baseline
- Date of birth
- Follow-up time
- Date of death
- Date of last follow-up
- Date of non-fatal event:
  - Hospitalization for heart failure
  - Non-fatal myocardial infarction (MI)
  - Acute coronary syndrome
  - Non-fatal stroke

2. Model used

«Linear Mixed Model». *Proc Mixed from SAS.*

The linear mixed model procedure allows correlated data with non-constant variability to be taken into account. The linear mixed model therefore offers the flexibility to model not only the means of the data, but also their variances and covariances. It also allows time-dependent explanatory variables (such as intercurrent events) to be taken into account. When reccurent events are recorded along follow up, they will be accounted for with repeated time-dependant covariate.

The model will be run on the complete data for each dimension of quality of life, after imputation following the imputation rules indicated by the developers of each questionnaire where applicable. Given missing data, which may vary from one dimension to another, even after imputation, the numbers may vary from one dimension to another.

a. Bivariate & Multivariate model: «Linear Mixed Model»

Application conditions

- Assumptions:
  - ❖ The dependent variable is considered to be linearly related to the fixed factor.
  - ❖ Fixed effects create an estimate of the mean of the dependent variable.
  - ❖ The dependent variable is also assumed to have a normal distribution.

    Note: in the event of non-normality of a quality-of-life score, we will run a generalized model instead.

Model fit quality

- A linear mixed model is one that includes both fixed and random effects.
- Fixed effects describe the relationships between the covariates and the dependent variable for an entire population.
- Random effects are sample-specific.
- The linear mixed model is written as follows:

$$\boldsymbol{Y = \beta X + \gamma Z + \epsilon}$$

- Fitting a linear mixed model enables us to estimate the mean of the coefficients $\boldsymbol{\beta}$ the vector of fixed-effect parameters and $\boldsymbol{\gamma}$ of the random effects parameter vector.
- By fitting a linear mixed model, we can also estimate the standard deviation of these coefficients across groups, as well as the standard deviation of individual observations from group means.

Parameter estimates will be reported with their probabilities.

Statistical tests will be two-sided, with alpha = 0.05 as the significance threshold. Each quality-of-life dimension of each questionnaire will be analyzed at this threshold, without correction for multiple testing, in line with standard practice in this field. In fact, the questionnaires are constructed in a paradigm of mutually independent dimensions.

For subjects with QoL data available after an intercurrent event, these events will be treated as time-dependent covariates.

In practice, we will carry out:

On the one hand, for each dimension of quality of life (SF-36, KD-QOL and Minnesota):

- *A model for each quality of life dimension (SF-36, KD-QOL and Minnesota) with a treatment group variable.*
- *A model for each quality of life dimension (SF-36, KD-QOL and Minnesota) with interaction between treatment group and measurement time.*
- *A model for each quality of life dimension (SF-36, KD-QOL and Minnesota) with treatment group variable and confounders.*
- *A model for each quality of life dimension (SF-36, KD-QOL and Minnesota) with treatment group-measurement time interaction and confounding factors.*
- *A model for each quality of life dimension (SF-36, KD-QOL and Minnesota) with treatment group variable, confounders, time-dependent variables and search for treatment group-factor interaction.*
- *A model for each QoL dimension (SF-36, KD-QOL and Minnesota) with treatment group variable, subgroup variables and treatment group-subgroup variable interaction.*

On the other hand, if a dimension of quality of life (SF-36, KD-QOL and Minnesota) is non-normal, ***a transformation by a Log function*** *will be performed.*

7. Sensitivity analysis

Sensitivity analysis will be performed for each dimension of quality of life, on complete and incomplete data even after imputation rules indicated by the developers of each questionnaire where applicable.

8. Latent Class Trajectory Model : « Group-Based Trajectory Modeling – GBTM »

- Trajectory profile for each dimension of Quality of Life (SF-36, KD-QOL and Minnesota) measured at baseline, 3 months, 1 year, 2 years, 3 years and 4 years.

Note: all patients with a missing Quality of Life (SF-36, KD-QOL and Minnesota) dimension at all follow-up times will be excluded from the latent class analysis.

a. Identification of Latent Class Trajectories

The various Latent Class Trajectories of each dimension of Quality of Life (SF-36, KD-QOL and Minnesota) are defined using Latent Class Trajectory Models, enabling us to obtain a variable in k trajectories from measured at baseline, 3 months, 1 year, 2 years, 3 years and 4 years.

1. Preliminary description and application conditions

- Measurement time metrics

  The time measurement will be indicated transparently and described briefly.

  Subjects with complete follow-up will be compared with those with incomplete on relevant characteristics. Significant variables be added as covariates in the Latent Class Trajectory Model.

2. Latent Class Trajectory Model

- These trajectories will be modeled:
  - With SAS, using Proc TRAJ (7), with the following parameters distribution ZIP (Zero Inflated Poisson) for modeling discrete quantitative variables.

- Model comparison and selection of the number of latent classes
  - Using Proc TRAJ in SAS:
    - Best model
      Present the evolutionary graph by class of the absolute absolute BIC (Bayesian Information Criterion) values of the Linear, Quadratic and Cubic models.

      Note: the best model is the curve model which lies above all the rest.

    - Selecting the number of latent classes
      The BIC (Bayesian Information Criterion) is the most suitable selection criterion.

    - The minimum number of patients in each trajectory should be at least 5% of the sample (8).

3. Qualitative characterization and labeling of trajectory classes: description of characteristics at baseline

- Identified trajectories will be described using a graphical representation of the graphical representation of the means (with 95% CI) of the different trajectory classes of the Kellgren stage over time (9) (=> Graph 1, produced using the SAS macro %TRAJPLOTNEW

b. Explanatory factors

- **Interest factor**
  - Treatment group (Spironolactone vs Placebo) (blind coded variable) [QL]
- **Confounding factors**
  - Age [QT]
  - Sex [QL]
  - Smoking [QL]
  - BMI [QT]
  - Center [QL]
  - Pre-existing CV disease [QL]
  - Pre-existing diabetes at baseline [QL]

c. Factors associated with profiles of each dimension of Quality of Life (SF-36, KD-QOL and Minnesota)

Bivariate & Mutltivariate analyses will be used to identify factors associated with profiles of each dimension of Quality of Life (SF-36, KD-QOL and Minnesota).

- If K classes =2: binary logistic regressions
- If K classes >2: there are several possibilities, depending on the trajectories identified and the objective sought:
  - Several binary logistic regressions with the same reference modality of trajectories
  - Ordinal logistic regression if trajectory classes are ordered
  - Bivariate & Multivariate multinomial logistic regression

The reference modality in these models is defined with the Methodologist and Clinician. If there is no preference, the reference modality will be the one with the largest number of employees.

1. List of variables

- **Variable to be explained:**
  - Profiles of each dimension of Quality of Life (SF-36, KD-QOL and Minnesota)

- **Explanatory factors**
  - **Interest factor**
    - Treatment group (Spironolactone vs Placebo) (blind coded variable) [QL]
  - **Confounding factors**
    - Age [QT]
    - Sex [QL]
    - Smoking [QL]
    - BMI [QT]

- Center [QL]
- Pre-existing CV disease [QL]
- Pre-existing diabetes at baseline [QL]

2. **Model used**

« Logistic regression model ». Proc logistic from SAS.

- **Bivariate & multivariate model: « Logistic regression model ».**

Application conditions

- Assumption of independence of observations.
- Assumption of logit linearity for quantitative variables.
  - Box-Tidwell test (addition of an interaction term X*ln(X) in the model): the significance of the interaction indicates a deviation from linearity.
  - Graphical method:
    Variable X divided into deciles

    Calculation of the proportion $\pi(X)$ of events observed for each decile each decile.

    - The graphical representation of $ln\left(\frac{\pi(X)}{1-\pi(X)}\right)$ 1-$\pi(X)$) as a function of the deciles should have a linear form.

- Model adequacy tests (Pearson or deviance): a significant test may indicate a deviation from linearity.

If the hypothesis is not valid for a quantitative variable X, we can transform it (X², X3,√X, ln(X),...) or discretize it into classes.

- **Model goodness of fit**

- Likelihood ratio test: a significant test indicates that the overall model is more informative than the null model.

- Hosmer-Lemeshow goodness-of-fit test: if the test is significant, the model model does not fit the data.

- The R² (Cox-Snell) and pseudo-R² (Nagelkerke), which summarize the proportion of variance variance explained by the model are indicators of model quality. The closer the R² is to 1, the better the model.

- ROC curve: the area under the ROC curve is an indicator of model quality. the closer the area under the curve is to 1, the better the model. model.

- Analysis of residuals can, if necessary, reveal outliers. individuals (outliers) that disrupt the construction of the model and model quality.

After the bivariate analysis, we need to select the variables that will enter the multivariate model with p<=0.2.

Important notes:

- *A model with profiles for each quality of life dimension (SF-36, KD-QOL and Minnesota) with a treatment group variable.*

- *A model with profiles for each quality of life dimension (SF-36, KD-QOL and Minnesota) with interaction between treatment group and measurement time.*

- *A model with profiles for each quality of life dimension (SF-36, KD-QOL and Minnesota) with treatment group variable and confounders.*

- *A model with profiles for each QoL dimension (SF-36, KD-QOL and Minnesota) with treatment group variable, subgroup variables and treatment group-subgroup variable interaction.*

9. Missing data

Imputation does not preserve relationships between variables, and can exert a considerable influence on the distribution of data. For this reason, missing data will not be imputed beyond the rules given by the questionnaire developers.

Statistical analyses will be carried out with **SAS/STAT 9.04.01**. Copyright © 2019 SAS Institute Inc-Cary, NC, USA.

Appendix 1

SF-36

Scoring sheet written by Marc SOUDANT

Inserm CIC1433 CIC-EC SeleQT

Description of SF-36 dimensions

Coding, recoding of items

Calculation of crude score (CS) taking into account missing data :

CS = mean of non-missing items*total number of items

Warning : Crude score can't be calulated if more than 50% of items are missing

Calculation of normalized score (NS) from 0 to 100 :

$NS = \{[(CS-C_{BP})/(C_{BM}-C_{BP})]*(N_{BM}-N_{BP})\}+N_{BP}$

C_{BP} et C_{BM} means respectively HRQoL's worst limit of and HRQoL's best limit of crude score

N_{BP} et N_{BM} means respectively HRQoL's worst limit of and HRQoL's best limit of normalized score

NS are normalized such as 0 = worst HRQoL et 100 = best HRQoL

Dimensions	Items	Modalities	Coding	Recoding	C_{BP}	C_{BM}	N_{BP}	N_{BM}
PF (physical functioning)	3 a-b-c-d-e-f-g-h-i-j	Yes, limited a lot	1		10	30	0	100
		Yes, limited a little	2					
		No, not limited at all	3					
RP (role-physical)	4	Yes	1		4	8	0	100
	a-b-c-d	No	2					
BP (bodily pain)	7	None	1	6	2	12	0	100
		Very mild	2	5.4				
		Mild	3	4.2				
		Moderate	4	3.1				
		Severe	5	2.2				
		Very severe	6	1				
	8	Not at all	1	6 if question 7 = 1 or missing				
				5 if question 7 = 2 to 6				
		A little bit	2	4.75 if question 7 missing				
				4 if question 7 = 1 to 6				
		Moderately	3	3.5 if question 7 missing				
				3 if question 7 = 1 to 6				
		Quite a bit	4	2.25 if question 7 missing				
				2 if question 7 = 1 to 6				
		Extremely	5	1				
MH (mental health)	9	All of the time	1	1	5	30	0	100
	b-c-f	Most of the time	2	2				
		A good bit af the time	3	3				
		Some of the time	4	4				
		A little of the time	5	5				
		None of the time	6	6				
	9	All of the time	1	6				
	d-h	Most of the time	2	5				
		A good bit af the time	3	4				
		Some of the time	4	3				
		A little of the time	5	2				
		None of the time	6	1				
RE (role-emotional)	5	Yes	1		3	6	0	100
	a-b-c	No	2					
SF (social functioning)	6	Not at all	1	5	2	10	0	100
		Slightly	2	4				
		Moderately	3	3				
		Quite a bit	4	2				
		Extremely	5	1				
	10	All of the time	1					
		Most of the time	2					
		Sime of the time	3					
		A little of the time	4					
		None of the time	5					
VT (vitality)	9	All of the time	1	1	4	24	0	100
	g-i	Most of the time	2	2				
		A good bit af the time	3	3				
		Some of the time	4	4				
		A little of the time	5	5				
		None of the time	6	6				
	9	All of the time	1	6				
	a-e	Most of the time	2	5				
		A good bit af the time	3	4				
		Some of the time	4	3				
		A little of the time	5	2				
		None of the time	6	1				

GH (general health)	1	Excellent	1	5	5	25	0	100
		Very good	2	4.4				
		Good	3	3.4				
		Fair	4	2				
		Poor	5	1				
	11	Définitely true	1	1				
	a-c	Mostly true	2	2				
		Dont't know	3	3				
		Mostly false	4	4				
		Definitely false	5	5				
	11	Définitely true	1	5				
	b-d	Mostly true	2	4				
		Dont't know	3	3				
		Mostly false	4	2				
		Definitely false	5	1				

Scoring of the physical (PCS) and Mental (MCS) Component Summary mesasures are calculated as

PCS = (PF_Z * 0.42402) + (RP_Z * 0.35119) + (BP_Z * 0.31754) + (SF_Z * -0.00753) + (MH_Z * -0.22069) + (RE_Z * -0.19206) + (VT_Z * 0.02877) + (GH_Z * 0.24954)

MCS = (PF_Z * -0.22999) + (RP_Z * -0.12329) + (BP_Z * -0.09731) + (SF_Z * 0.26876) + (MH_Z * 0.48581) + (RE_Z * 0.43407) + (VT_Z * 0.23534) + (GH_Z * -0.01571)

where :

PF_Z = (PF - 84.52404) / 22.89490

RP_Z = (RP - 81.19907) / 33.79729

BP_Z = (BP - 75.49196) / 23.55879

GH_Z = (GH - 72.21316) / 20.16964

VT_Z = (VT - 61.05453) / 20.86942

SF_Z = (SF - 83.59753) / 22.37642

RE_Z = (RE - 81.29467) / 33.02717

MH_Z = (MH - 74.84212) / 18.01189

KD-QOL

Scoring sheet written by Teresa GAROT

Inserm CIC1433 CIC-EC SeleQT, seleqt.univ-lorraine.fr

Description of KDQOL_L dimensions

Coding, recoding of items

Calculation of crude score (CS) taking into account missing data :

CS = mean of non-missing items*total number of items

Warning : Crude score can be calulated if at least 50% of items are non missing

Calculation of normalized score (NS) from 0 to 100 :

$NS = \{[(CS-C_{BP})/(C_{BM}-C_{BP})]*(N_{BM}-N_{BP})\}+N_{BP}$

C_{BP} et C_{BM} means respectively HRQoL's worst limit of and HRQoL's best limit of crude score

N_{BP} et N_{BM} means respectively HRQoL's worst limit of and HRQoL's best limit of normalized score

NS are normalized such as 0 = worst HRQoL et 100 = best HRQoL

Dimensions	Items	Modalities	Coding	Recoding	C_{BP}	C_{BM}	N_{BP}	N_{BM}
Burden of kidney disease	12a,12b,12c, 12d	Definitely true	1	0	0	400	0	100
		Mostly true	2	25				
		Don't know	3	50				
		Mostly false	4	75				
		Definitely false	5	100				
Symptoms/Problems	14a,14b,14c, 14d,14e,14f, 14g,14h,14i,14j,14k,14l or 14m**	Not at all bothered	1	100	0	1200	0	100
		Somewhat bothered	2	75				
		Moderately bothered	3	50				
		Very much bothered	4	25				
		Extremely bothered	5	0				
Effects of kidney disease on daily life	15a,15b,15c, 15d,15e,15f, 15g,15h	Not at all bothered	1	100	0	800	0	100
		Somewhat bothered	2	75				
		Moderately bothered	3	50				
		Very much bothered	4	25				
		Extremely bothered	5	0				

MINNESOTA

Scoring sheet written by : Lorraine BERNARD
Inserm CIC1433 CIC-EC SeleQT

Description of MINNESOTA LIHFE dimensions
Coding, recoding of items

Calculation of crude score (CS) taking into account missing data (no recommendatic
CS = mean of non-missing items*total number of items
Warning : Crude score can't be calulated if more than 50% of items are missing

Calculation of normalized score (NS) from 0 to 100 :

$NS = \{[(CS-C_{BP})/(C_{BM}-C_{BP})]*(N_{BM}-N_{BP})\}+N_{BP}$

CBP et CBM means respectively HRQoL's worst limit of and HRQoL's best limit of crude score
NBP et NBM means respectively HRQoL's worst limit of and HRQoL's best limit of normalized score
NS are normalized such as 0 = worst HRQoL et 100 = best HRQoL

Dimensions	Items	Modalities	Coding	C_{BP}	C_{BM}	N_{BP}	N_{BM}
Physical	2, 4, 5, 7, 8, 9, 11, 13	No	0	40	0	0	100
		Very Little	1				
		|	2				
		|	3				
		|	4				
		Very Much	5				
Mental	14, 16, 17, 21	No	0	20	0	0	100
		Very Little	1				
		|	2				
		|	3				
		|	4				
		Very Much	5				
Social	3, 12, 19	No	0	15	0	0	100
		Very Little	1				
		|	2				
		|	3				
		|	4				
		Very Much	5				
Incapacity	6, 10, 15, 20	No	0	20	0	0	100
		Very Little	1				
		|	2				
		|	3				
		|	4				
		Very Much	5				

Note: items 1 and 18 did not participate for the 4 dimensions but participate for the total score

The numbering of items corresponds to the French questionnaire
Another version of the scoring manual with items according to the English questionnaire is avalaible

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