DETAILED STATISTICAL ANALYSIS PLAN (SAP)

Fibrosis, inflammation, Oxygenation of Renal Tissue In FabrY disease: The FORTIFY study

Contents

1. Administrative information

1.1. Title, registration, version and revisions

Full study title	Fibrosis, inflammation, Oxygenation of Renal Tissue In FabrY disease: The FORTIFY study
Acronym	FORTIFY
Local project number	102417 / H-23035668
Clinicaltrials.gov number	Provided when registered
Study protocol version	1.1.3 (14.07.2023)
SAP version	1.1.1 (14.01.2024)

1.2. Revision history

SAP revision history	None
SAP revision justification	-
SAP revision timing	-

1.3. Roles and responsibility

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Contributors and roles	-
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1.4. Signatures

We the undersigned, certify that we read this SAP and approve it as adequate in scope of the main-analyses of the FORTIFY study.

1.4.1. Author

Name: Niels H. Brandt-Jacobsen

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Date:

1.4.2. Principle investigator

Name: Caroline M. Kistorp

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Date:

1.5. Abbreviations

2. Introduction

This document outlines the statistical methods to be implemented during the analyses of data collected within the scope of Fibrosis, inflammation, Oxygenation of Renal Tissue In FabrY disease (the FORTIFY study). The purpose of this SAP is to provide a framework in which answers to the protocol objectives may be achieved in a statistically rigorous fashion, without bias or analytical deficiencies. Specifically, this plan has the following purposes:

- To outline the specific types of analyses and presentations of data prospectively that will form the basis for conclusions.
- To explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analysis. Any deviations from these guidelines must be substantiated by sound statistical reasoning and documented in writing in the final study report.

2.1. Background and rationale

Fabry disease is a rare X-linked lysosomal disorder. An enzyme deficiency causes progressive accumulation of glycosphingolipids in virtually all organs, leading to dysfunction and eventually organ failure. Although, Fabry disease is caused by an X-linked genetic mutation both males and females [1]. Women present with a more heterogenous degree of organ involvement, however, all patients are at increased risk of multisystem organ involvement and must attend extensive screening, continuous monitoring in order to decide when and who are in need of treatment [2]. As evident in patients who presents with no or very low enzyme activity, early multi-organ involvement of the greatest prognostic impact is loss of kidney function [1].

Fabry nephropathy is characterized by the accumulation of Gb3 deposition in renal cells, where kidney biopsies suggest healthy, functioning tissue is substituted with reparative diffuse fibrosis [3–5]. However, Gb3 accumulation in Fabry disease accounts for less than 5% of the total tissue volume at maximum [6,7], the disproportionate and devastating effects observed have led to the proposal of Gb3 having additional effects beyond mere storage [8–11]. Oxidative stress, endothelial dysfunction, and inflammation have been proposed as important mechanisms induced directly or indirectly by Gb3 accumulation [9–12].

Renal hypoxia is now considered to play a key role in the development of chronic kidney disease (CKD) [13–17]. Using a novel contrast-free, non-invasive magnetic resonance imaging (MRI) enables us to investigate the pathological mechanisms underlining Fabry nephropathy by measurements of oxygenation, inflammation and fibrosis [13–16]. Therefore, this novel method provides information on kidney-specific shift in energetic oxygen-dependent capacity, ongoing inflammation, and

accumulation of fibrosis, with changes not only portraying key aspects of kidney physiology, but changes expected to elucidate on the pathophysiology forming the very basis of Fabry nephropathy.

While the recent advances in imaging present a unique possibility for early detection of Fabry nephropathy, validation is needed to establish the high-precision diagnostic of MRI against clinically established biomarkers of risk such as pathologically increased UACR – the currently recommended parameter of renal risk in Fabry nephropathy [4,5,18–21].

2.2. Objectives

2.2.1. Objectives and research questions

The overall objective of this study is to investigate Fabry-associated renal organ involvement by using a novel magnetic resonance imaging (MRI) approach, focusing on changes in renal oxygen levels by blood oxygenation-level dependent (BOLD) imaging. Centering around the question of whether impaired renal oxygenation can be an early characteristic of Fabry nephropathy, which precedes established markers of renal decline such as estimated glomerular filtration rate or urinary albumin/creatinine ratio (UACR). Furthermore, we aim to correlate renal oxygenation to the phenotypic presentation of patients with Fabry-associated nephropathy regarding circulating and imaging-derived biomarkers of kidney inflammation, fibrosis and injury as compared with healthy age- and sex-matched controls.

1. Using a non-invasive, contrast-free MRI protocol focusing on parameters of oxygenation, does patients with Fabry disease exhibit increased levels of MR-based measures of inflammation, fibrosis, and injury in the kidney?
2. Using an extensive, in-depth biomarker blood panel to investigate the pathological pathways associated, how does patients with Fabry disease and Fabry-associated nephropathy correlate to levels of renal involvement?

2.2.2. Hypotheses

The hypothesis of research question 1, *hereafter the renal study*, is:

- Null hypothesis: there is no true correlation between any Fabry disease and MR-based renal impairment – mainly focusing on renal oxygenation, but also including inflammation, fibrosis, and renal injury.
- Alternative hypothesis: MR-based renal impairment – mainly focusing on renal oxygenation, but also including inflammation, fibrosis, and renal injury – is associated with the presence of Fabry disease.

As research question 2, hereafter *the biomarker study*, is exploratory in nature no formal hypothesis

2.2.3. Scope

This SAP will be the guiding document, creating the outline for the analyses that will be conducted throughout the study. Any additional aims will be included in an appendix of this SAP as an addendum in the future and be added in the revision history of the document (section 1.2).

3. Study methods

3.1. General study design and plan

The study is initiated by Caroline Kistorp, professor at the Danish National Fabry Centre, at the Department of Hormone and Metabolism, Copenhagen University Hospital - Rigshospitalet. The FORTIFTY study is a cross-sectional study and therefore purely observational in nature. No interventions are used as part of study design.

The study will consist of a group of patients with genetically verified Fabry disease. Furthermore, a control group of healthy age- and sex-matched individuals will be included to comprise a contemporary control cohort and will undergo the same program.

The protocol of this study was reviewed and approved by the regional scientific ethics committee (Project number: 102417 / H-23035668) and registered at clinicaltrials.gov prior to the inclusion of the first patient into the study. The original SAP was written prior to the enrollment of the first patient, with revisions and timing of revisions evident in the revision history (section 1.2).

3.2. Sample size, power, and detectable difference

Use of the specified MR-based renal imaging parameters has not previously been investigated in patients with Fabry disease prior to the initiation of the current study. This makes it difficult to calculate sample size based on previous literature.

3.2.1. The renal study

From our previous study investigating patients with type I diabetes and renal impairment, we found that the mean baseline oxygenation (R2*) was 23 with (SD=4) [22]. A between-group difference in R2* of 2.0 units can be considered a clinically important difference.

In the cohort, a difference of 2.0 units, an SD of the difference of 2, 80% power, a type 1 error of 5%, and wanting to compare groups of patients with Fabry disease independently results in a need of allocating 17 participants in each group. The addition group of healthy age- and sex-matched controls results in the enrollment of 51 participants. Accounting for incident claustrophobia causing an incomplete acquisition of data, we aim to include 20:20:20 participants (Fabry w/ renal impairment; Fabry w/o renal impairment; age- and sex-matched controls).

3.2.2. Biomarker study

Recognizing the exploratory nature of biomarker study, no formal hypothesis is pre-specified as part of the statistical analysis plan, thus a sample size calculation is not pre-specified. Results based on these analysis are therefore perceived as hypothesis-generating.

3.2.3. Additional considerations

The current study is an observational cross-sectional study, and the power calculation is performed to investigate the relationship between the presence of renal impairment with the phenotypic presentation of Fabry nephropathy. As the total Danish National currently consists of 100 individuals, of which approximately 40% have a history albuminuria, a study size consisting of 40 patients with genitically-verified Fabry disease is feasible in the current patient population.

3.3. Timing of final analysis

Data cleansing and MR image validation will be performed upon completion of the last patient included in the study. The final analysis will be conducted hereafter.

This statistical analysis plan was added to the study protocol at clinicaltrials.gov, before the first patients first visit, and revisions are performed prior to the closure of the database and before any analyses had been conducted.

4. Statistical principles

4.1. Multiplicity

The renal study consists of one primary outcome, and one or more secondary, and one or more exploratory outcomes. As we have only one primary endpoint, renal oxygenation in Fabry disease between groups with and without renal impairment, the primary endpoint will be reported as is and not be subject to p-value adjustment. However, we will encounter multiplicity issues due to the multiple secondary and exploratory outcomes that are tested for significance in the same cohort (table 1, section 7).

The study measures nine pre-defined as key secondary outcomes (table 2, section 7). These outcomes will be subject to adjustment for multiplicity as part of standard reporting, reported as a supplementary analysis to assess the robustness of the conclusions drawn from these results. The remaining outcomes of the renal study and outcomes of the biomarker study will be reported as exploratory and will not be subject to subject to adjustment for multiplicity.

4.1.1. Adjustment procedure

We will apply an adjustment for multiplicity using the False Discovery rate-adjustment proposed by Benjamini-Hochberg [23], adjustning the p-values of key secondary. The adjustment procedure will be performed as a supplementary analysis, reporting unadjusted and adjusted p-values in order to create full transparency of the statistical procedure and the strength of the analyses performed.

4.2. Statistical significance and confidence interval

An unadjusted p-value below 0.050 will be reported as achieving nominal statistical significance for both our primary outcome and key secondary outcomes. Regarding results of key secondary outcomes, an adjusted p-value below 0.050 will be reported as robust. To account for discrepancies due to multiplicity adjustment, results which achieve nominal statistical significance (unadjusted p-value below 0.050), but fail to be proven robust (adjusted p-values above 0.050) will highlighted to emphasize the increased chance of a type I error.

Results will be presented with their values (e.g. regression coefficients, mean difference etc.) with 95% confidence intervals.

4.3. Adherence and protocol deviations

4.3.1. Definitions of protocol deviations

Protocol deviations are defined as the activities which diverge from the protocol approved by the local institutional review board.

5. Study population

5.1. Screening data

Eligible patients who were not included will be summarized as to the reason of exclusion.

5.2. Eligibility

All eligible patients have a genetically-verified diagnosis of Fabry disease and are currently followed at the National Fabry Center, Copenhagen University Hospital - Rigshospitalet. Review of eligibility and inclusion in the study consisted of a protocolized clinical examination and subsequent blood and urine analysis. Review is performed by study personnel.

5.2.1. Inclusion criteria – Fabry cohort

- Male and female individuals with a genetically-verified diagnosis of Fabry disease
- ≥ 18 years of age.
- Able to give informed consent

5.2.2. Exclusion criteria – Fabry cohort

- Any contraindication for magnetic resonance imaging according to standard checklist used in clinical routine, including claustrophobia or metallic foreign bodies, metallic implants, internal electrical devices, or permanent makeup/tattoos that cannot be declared MR compatible.
- Pregnancy

The Fabry cohort will further grouped by presence of renal impairment as depicted by the CKD-EPI classification (≥ CKD G2/A1).

5.2.3. Inclusion criteria – Control cohort

- Male and female individuals (≥18 years of age)
- Able to give informed consent

5.2.4. Exclusion criteria

- A genetically-verified diagnosis of Fabry disease.
- Family member to a patient with a genetically-verified diagnosis of Fabry disease
- Cancer expected to influence life expectancy.
- Known heart failure, previous apoplexia or previously established kidney disease.
- Initiation or change of antihypertensive therapy within 3 months of enrolment
- Renal impairment as depicted by the CKD-EPI classification (≥ CKD G2/A1)
- Any contraindication for MRI according to standard checklist used in clinical routine, including claustrophobia or metallic foreign bodies, metallic implants, internal electrical devices, or permanent makeup/tattoos that cannot be declared MR compatible.

- Pregnancy

5.3. Recruitment

A flow diagram will be used to visualize the flow of patients. In this flow diagram, we will report the population from which the eligible patients were selected, reasons for exclusion and measurements were validated.

5.4. Baseline patient characteristics

5.4.1. Collected baseline patient characteristics

The cohort study was designed to register a set of clinical examination, biochemical and renal imaging variables in each included patient. We extracted baseline demographic data by semi-structured clinical interview and examination. We obtained the biochemical values from analyses on venous blood and urine samples acquired at the day of inclusion in the study. Finally, renal imaging variables are obtained by MRI – all at a single visit (**Table 1** provides an overview of all collected variables and indicates for each variable whether it is categorised as a clinical examination, renal imaging, or biochemical variable).

5.4.2. Descriptive summarization of baseline patient characteristics

We will list general patient characteristics in a baseline characteristics table. Data will be presented as mean with standard deviation (SD) when normally distributed or as median with interquartile range in case of skewed data. Dichotomous and categorical data will be presented in proportions. Normality of the data will be assessed using P-P plots, Q-Q plots, and histograms. Linearity will be assessed using scatter plots. Differences between continuous variables will be assessed using Student's t-tests or Mann-Whitney-U test, depending on normality, whereas the Fischer's exact test will be used for categorical values. Acquisition of repeated measurements at different timepoints is not part of the study design.

5.5. Assumed confounding covariates

Given the size of the study, confounding factors – measured or unmeasured – may provide variation, where model adjustment may prove difficult. The greatest factors, which may skew our results (age, sex, known pathogenic vs late onset-variant) are predefined covariates to be used in a supplementary adjusted model. Although, the individual genetic variant inevitably will be a factor with possible influence on the analyses, the available cohort does not allow for stratification of the cohort beyond the use 'known pathogenic' and 'known late onset'.

While further measured and unmeasured variables, such as environmental, genetic, or psychological factors, may influence the analyses, further confounding results will not be prespecified, but added post hoc.

6. Analysis

6.1. Outcome definitions

The focus of the study is the MR-based renal imaging study.

6.1.1. Primary outcomes

- A between-group difference in renal hypoxia (R*) evaluated by BOLD MRI when comparing the groups of patients with Fabry disease.

6.1.2. Key secondary outcomes

- A between-group difference in renal hypoxia (R*) evaluated by BOLD MRI when comparing patients with Fabry disease irrespective of renal impairment with the control group.
- A between-group difference in perfusion of the renal cortex (mL/100g/min) when comparing patients with Fabry disease with the control group.
- A between-group difference in perfusion of the renal medulla (mL/100g/min) when comparing groups with Fabry disease patients with the control group.
- A between-group difference in renal blood flow (mL/min) when comparing groups with Fabry disease patients with the control group.
- A between-group difference in native T1 (ms) when comparing groups with Fabry disease patients with the control group.
- A between-group difference in diffusion-weighted signaling when comparing groups with Fabry disease patients with the control group.

6.2. Analysis methods

6.2.1. Primary analysis

The primary analysis will be tested using an unadjusted linear model with the variables stated above as outcome-variables and the grouping variable as explanatory variable according to the above mentioned. The statistical analysis will use all available information.

6.2.2. Linear correlations between variables

Correlation between variables will be tested using a linear model, reporting coefficients, 95% confidence intervals, p-values. The statistical analysis will use all available information.

6.3. Sensitivity and subgroup analyses

Sensitivity analyses will be performed by adjusting for the model with pre-specified confounding variables (age, sex, pathogenic variant). Although the overall statistical power is low, the value of the results supersedes the interferential power due to the scarcity of evidence specific to Fabry disease. Therefore, subgroup analyses will be performed on an exploratory basis. Pre-defined subgroups include sex (male vs female), receiving of Fabry-specific treatment (yes vs. no), known pathogenic

variant (yes vs no), presence of albuminuria (yes vs no), renal impairment (≥ CKD G3a/A2).

6.4. Missing data

6.4.1. Reasons for missing data

We expect to have no missing data for the easy-accessible clinical variables such as blood pressure, heart rate, blood, and urine sampling. However, in case of patient claustrophobia or discomfort during renal MRI scans, the imaging protocol can be terminated per the request of the patient, causing an inevitable loss of data.

Although the sample size has been calculated to mitigate these effects, a comparison will be performed, comparing patients who undergo the full imaging protocol vs patient who do not. As the overall ability to undergo renal imaging is not dependent on renal impairment, the reasons for missingness are viewed to be missing at random (MAR) or missing completely at random (MCAR), having little influence the overall conclusions of the study.

6.4.2. Imputation method

Our primary model analysis will not rely on imputation; however, a supplementary sensitivity analysis may be performed to investigate the influence of patients who do not undergo a partial renal imaging protocol. Multiple imputation using the MI impute command in SAS will be used. Included in the imputation procedure will be all available imaging variables, weight, height, age, sex, and all blood- and urine-variables. The random seed used will be (45361) with imputation repeated 50 times or more until the estimates are deemed stable.

6.5. Statistical software

Statistical analyses will be performed using SAS version 9.4(SAS institute, Cary, NC, USA).

7. Tables and figures

Table 1. Overview of all pre-specified outcomes measured in the renal study and biomarker study.

	Examinations
Clinical examination	
	Sex
	Age
	Genetic variant
	Height
	Weight
	Waist circumference
	Hip circumference
	Electrocardiogram
	Office blood pressures
	Pulse (Office blood pressure)
	Mainz Severity Score Index
	Fabry International Prognostic Index
	SF36 Quality of Life-questionnaire
Renal imaging	
	Renal cortical oxygenation
	Renal medullar oxygenation
	Renal cortical perfusion
	Renal medullar perfusion
	Renal blood flow
	Renal T1-values
	Renal diffusion-values
	Renal cortical oxygenation post-hyperoxygenation
	Renal medullar oxygenation post-hyperoxygenation
	Renal cortical perfusion post-hyperoxygenation
	Renal medullar perfusion post-hyperoxygenation
	Renal blood flow post-hyperoxygenation
Biomarker analysis	
	α-gal A activity in leucocytes
	Lyso-Gb3
	Gb3
	urine Gb3
	Creatinine
	GDF-15
	TGF-β
	FGF-21
	FGF-23
	VEGF
	Collagens
	fasting plasma glucose
	Insulin
	3-OH-hydroxybutyrate
	HbA1c
	lipid profile
	NT-proBNP
	TnI
	hsTnT
	proANP

	proCNP
	urinary podocyte excretion,
	Urinary albumin/creatinine ratio

Table 2. Overview of all pre-specified primary and key secondary outcomes measured in the renal study.

Examination	**Primary outcome (P) or key secondary outomes (S)**
Renal oxygenation	
Between Fabry groups	P
Between Fabry and controls	S
Renal perfusion	
Between Fabry groups	S
Between Fabry and controls	S
Renal blood flow	
Between Fabry groups	S
Between Fabry and controls	S
Renal T1-values	
Between Fabry groups	S
Between Fabry and controls	S
Renal diffusion-values	
Between Fabry groups	S
Between Fabry and controls	S

The study includes one primary outcome and nine key secondary outcomes. Key secondary outcomes will be subject to p-value adjustment to assess the robustness of the conclusions based on the results, reporting both unadjusted and adjusted p-values. Any other pre-specified or post hoc analyses performed will not be subject to p-value adjustment.

8. References

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