STATISTICAL ANALYSIS PLAN for Effect of treatment of sleep apnea in patients with paroxysmal atrial fibrillation.

Effect of Treatment of Sleep Apnea in Patients with Paroxysmal Atrial Fibrillation

Statistical Analysis Plan

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SIGNATURE PAGE

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ABBREVIATIONS

AE	Adverse Event
AF	Atrial fibrillation
ATC	Anatomical/Therapeutic/Chemical
BMI	Body Mass Index
BPM	Beats Per Minute
CI	Confidence Interval
CPAP	Continuous positive airway pressure
CRP	C-reactive protein
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
ESS	Epworth Sleepiness Scale
FOSQ	Functional Outcomes in Sleep Questionnaire
MCP	Monocyte Chemoattractant Peptide
MedDRA	Medical Dictionary for Regulatory Activities
NT-proBNP	N-terminal pro-brain natriuretic peptide
OSA	Obstructive Sleep Apnea
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SD	Standard Deviation
SOC	System Organ Class
TIMP	Tissue Inhibitor of Metalloproteinase
TNF	Tumor Necrosis Factor

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1 Introduction

1.1 Background and rationale

Atrial fibrillation is associated with increased mortality as well as morbidity. There is strong evidence for an association between atrial fibrillation and sleep apnea. It is not known if treatment of sleep apnea with continuous positive airway pressure (CPAP) will reduce the burden of atrial fibrillation.

1.2 Trial Objectives

1.2.1 Primary Objective

To investigate the effect of CPAP on atrial fibrillation burden in patients with paroxysmal atrial fibrillation and concomitant moderate-severe sleep apnea.

1.2.2 Secondary Objectives

To investigate the effect of CPAP on atrial fibrillation symptom burden, quality of life, sleep quality and symptoms of obstructive sleep apnea.

1.2.3 Exploratory Objectives

To investigate the effect of CPAP on cardiac structure, biomarkers, gene expression of white blood cells, lung function, and body composition. We will also investigate activity patterns around the onset of atrial fibrillation.
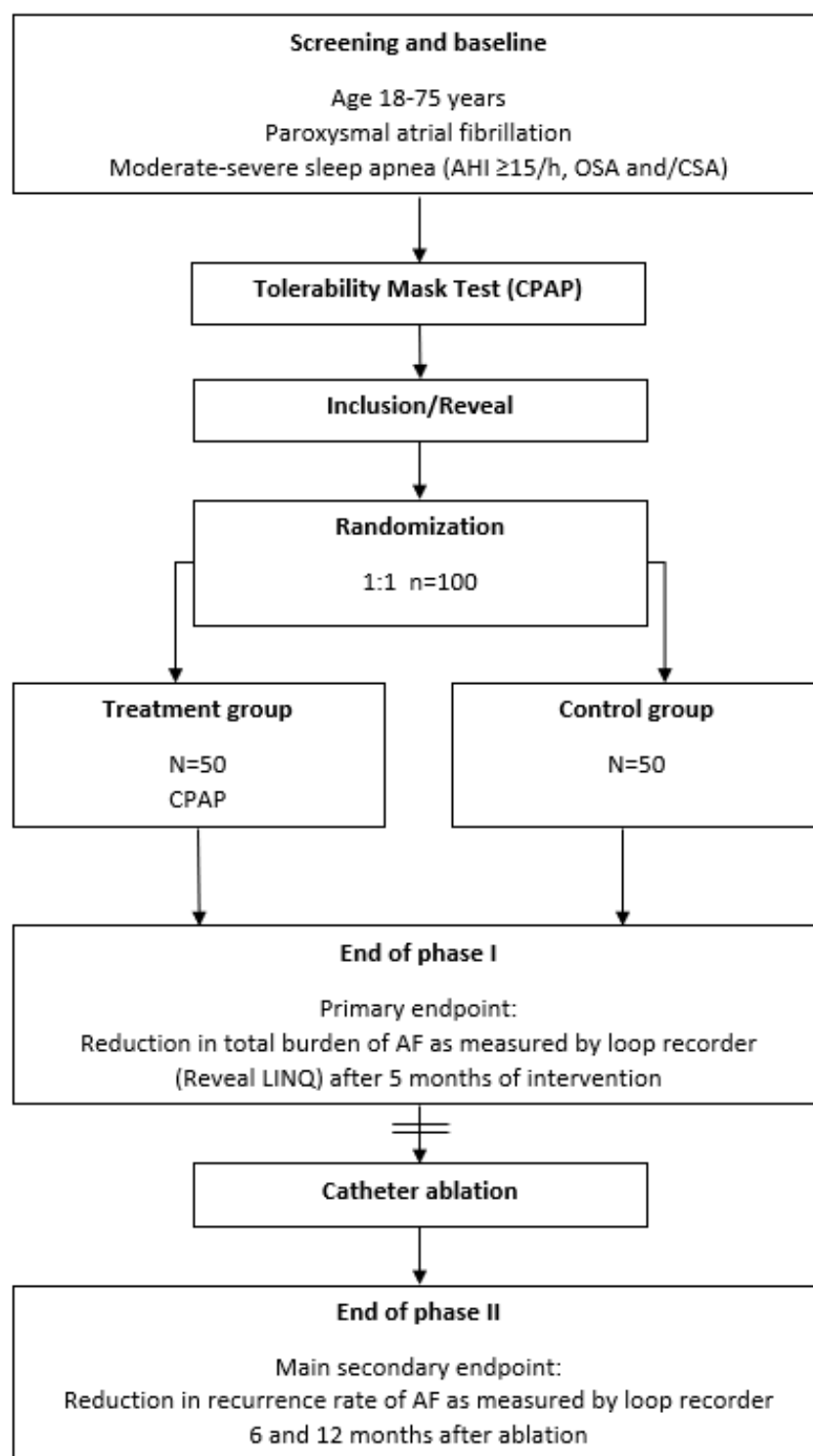
2 Trial Methods

2.1 Trial Design

The A3 study is a randomized, controlled, open-label, parallel group trial being conducted at St Olavs University Hospital, Trondheim and Oslo University Hospital, Rikshospitalet, Oslo. Patients will be randomized in a 1:1 ratio to CPAP (the intervention) or control group (50 patients in each arm). The effects of CPAP treatment on atrial fibrillation will be determined using an implanted loop recorder (Reveal LINQ™, Medtronic) that detects all arrhythmia episodes. The primary endpoint is the reduction of the total burden of atrial fibrillation after 5 months of follow-up (preablation, Phase 1 of the study). Reduction in the recurrence rate after ablation is the main secondary endpoint (Phase 2 of the study). All patients will be followed up for 12 months after ablation.

This statistical analysis plan covers Phase 1 of the study. There will be a separate statistical analysis plan for Phase 2 of the study.

Figure: Flow chart. Phase 1 of the study ends after 5 months of intervention.

STATISTICAL ANALYSIS PLAN for Effect of treatment of sleep apnea in patients with paroxysmal atrial fibrillation.

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│                   Screening and baseline                  │
│                                                           │
│                    Age 18-75 years                        │
│               Paroxysmal atrial fibrillation              │
│       Moderate-severe sleep apnea (AHI ≥15/h, OSA and/CSA) │
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                 ┌─────────────────────────────┐
                 │  Tolerability Mask Test (CPAP) │
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                 │       Inclusion/Reveal        │
                 └─────────────────────────────┘
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                 ┌─────────────────────────────┐
                 │        Randomization          │
                 │                               │
                 │         1:1  n=100            │
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                   │                       │
                   ▼                       ▼
        ┌────────────────────┐   ┌────────────────────┐
        │  Treatment group    │   │   Control group     │
        │                     │   │                     │
        │       N=50          │   │       N=50          │
        │       CPAP          │   │                     │
        └────────────────────┘   └────────────────────┘
                   │                       │
                   ▼                       ▼
        ┌─────────────────────────────────────────────┐
        │                End of phase I                 │
        │                                               │
        │              Primary endpoint:                │
        │  Reduction in total burden of AF as measured  │
        │  by loop recorder (Reveal LINQ) after 5       │
        │  months of intervention                       │
        └─────────────────────────────────────────────┘
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                 │       Catheter ablation       │
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        ┌─────────────────────────────────────────────┐
        │                End of phase II                │
        │                                               │
        │            Main secondary endpoint:           │
        │  Reduction in recurrence rate of AF as        │
        │  measured by loop recorder                    │
        │  6 and 12 months after ablation               │
        └─────────────────────────────────────────────┘
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STATISTICAL ANALYSIS PLAN for Effect of treatment of sleep apnea in patients with paroxysmal atrial fibrillation.

2.2 Randomisation

Eligible patients are allocated in a 1:1 ratio between CPAP-treatment and control. The randomization list will be generated using Stata (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP) with a 1:1 allocation using random block sizes of 4, 6, 8, and 10. Patients will be assigned a unique patient identification number.

Randomization and allocation to treatment or control arm is being done using the online platform ViedocTM (PCG Solutions, Uppsala, Sweden) and will take place one month after implantation of a subcutaneous arrhythmia detector (RevealLINQ™, loop recorder, Medtronic).

2.3 Sample size

The primary endpoint is a reduction of AF burden (% of time in AF) in the intervention group compared to control. We have defined a 25 % reduction of AF burden (% of time in AF) as a clinically significant effect. The extent to which treatment of AF will improve SA is unclear, and there are few data on the effects of treating SA on arrhythmia burden in patients with AF. With a mean time of 34% in atrial fibrillation and a standard deviation (SD) of 12%,[1] a power of 80% and a two-sided significance level of 5 % we will need at least 33 patients in each group. To allow for an increase in the standard deviation to 15%, we will include a total of 100 patients. No interim analysis will be performed.

2.4 Statistical Framework

2.4.1 Hypothesis Test

This trial is designed to establish the superiority of treatment of CPAP over usual care for the total burden of atrial fibrillation in patients with paroxysmal atrial fibrillation and concomitant moderate-severe sleep apnea.

- The primary null hypothesis is that the change in the total burden of atrial fibrillation from baseline (one month prior to randomization) to the last three months of the intervention period is equal with CPAP treatment and usual care.
- The primary alternative hypothesis is that there is a difference in change in the total burden of atrial fibrillation from baseline (one month prior to randomization) to the last three months of the intervention period between CPAP treatment and usual care.

There is only one identified primary analysis in this trial. All other efficacy analyses will be regarded as supportive or exploratory.

2.4.2 Decision Rule

This trial is designed to address a single primary outcome. Superiority of either CPAP or usual care is claimed if the primary null hypothesis is rejected on the significance level (alpha) of 0.05 (two-sided).

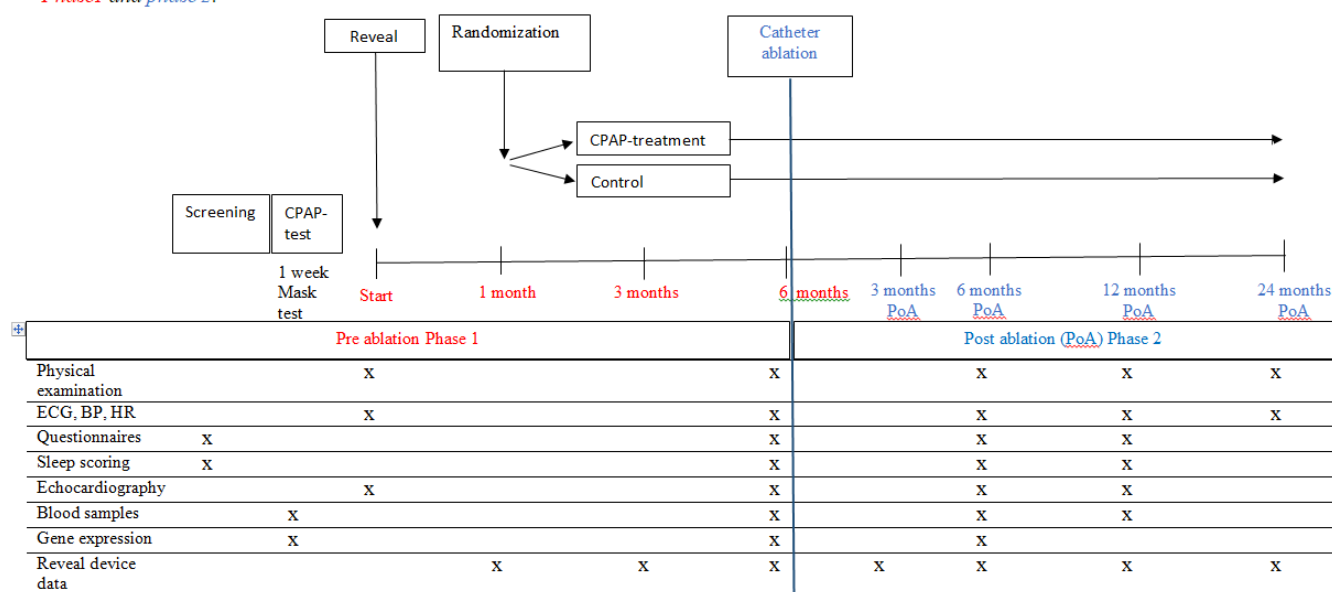## 2.5 Statistical Interim Analyses and Stopping Guidance

There will be no interim analyses in this trial.

2.6 Timing of Final Analysis

The final analysis will be performed when all patients have concluded 5 months of intervention in Phase 1 of the study.

2.7 Timing of Outcome Assessments

Phase1 and *phase 2:*

	Pre ablation Phase 1				Post ablation (PoA) Phase 2			
Physical examination		x		x		x	x	x
ECG, BP, HR		x		x		x	x	x
Questionnaires	x			x		x	x	
Sleep scoring	x			x		x	x	
Echocardiography		x		x		x	x	
Blood samples	x			x		x	x	
Gene expression	x			x		x		
Reveal device data		x	x	x	x	x	x	x

3 Statistical Principles

3.1 Confidence Intervals and p-values

All calculated p-values will be two-sided and compared to a 5% significance level. If a p-value is less than 0.05, the corresponding treatment group difference will be denoted as statistically significant. All efficacy estimates will be presented with two-sided 95% confidence intervals. As there is only one primary null hypothesis to be tested in this trial, there will be no adjustments for multiplicity.

3.2 Adherence

3.2.1 Adherence to Allocated Treatment

CPAP therapy will be monitored remotely using AirView™ (ResMed) and in addition data will be downloaded from the device SD card every three months. The data will be downloaded in the ResScan software program for compliance calculations.

Adherence to the intervention will be presented as mean (±SD) duration of adherence to CPAP therapy in the last three months of treatment before ablation procedure (period of primary endpoint). The residual apnea-hypopnea index during CPAP use, as measured by the CPAP device will also be presented as average events per hour.

The number and % of participants using the CPAP device more than four hours per night will be presented.

3.3 Analysis Populations

The Enrolled set will include all patients who have provided informed consent and have been included into the study data base.

The Full Analysis Set (FAS) will be defined as all patients randomly assigned to a treatment group.

The Per Protocol Set (PPS) will include all randomised patients who have at least one assessment of the efficacy variable burden of atrial fibrillation, are on their randomized treatment CPAP or usual care. In the CPAP group, patients with no duration of the CPAP device the last three months will be excluded for the PPS.

4 Trial Population

4.1 Screening Data, Eligibility and Recruitment

The total number of screened patients and reasons for not entering the trial will be summarised and tabulated.

A CONSORT flow diagram (appendix A) will be used to summarise the number of patients who were:

- assessed for eligibility at screening
- eligible at screening
- ineligible at screening*
- eligible and randomised
- eligible but not randomised*

- received the randomised allocation
- did not receive the randomised allocation*
- lost to follow-up*
- discontinued the intervention*
- randomised and included in the primary analysis
- randomised and excluded from the primary analysis*

*reasons will be provided.

4.2 Withdrawal/Follow-up

The number of withdrawals will be presented.

A withdrawal is defined as participants who withdrew consent, and for which data collected cannot be used.

A lost to follow up is defined as participants who withdrew from follow-up, but allowed data collected to be used.

The status of eligible and randomised patients at trial end will be tabulated by treatment group according to

- completed intervention and assessments
- completed assessments but not intervention
- withdrew consent
- lost to follow-up

4.3 Baseline Patient Characteristics

The following patient demographics and baseline characteristics will be summarised:

Age, years
Gender, no. (%)
BMI, kg/m²
Neck circumference, cm
Waist-to-hip ratio
LVEF, %
AHI, per hour
Obstructive apnea index, per hour
Central apnea index, per hour
Minimum SpO$_2$, %
SpO$_2$ time < 90%, %
Epworth Sleepiness score
FOSQ score

SF-36 (Physical and Mental Component Summary)

Cardiovascular disease, no. (%)

Hypertension no. (%)

Diabetes mellitus no. (%)

Stroke/TIA no. (%)

COPD/asthma no. (%)

Previous DC cardioversion no. (%)

Beta-blocker no. (%)

ACE-I + ARB no. (%)

Calcium channel blocker no. (%)

Diuretic no. (%)

Statin no. (%)

NOACs no. (%)

Antidiabetic medication no. (%)

Flecainide no. (%)

Dronedarone no. (%)

Hb, g/dl

Creatinine, mcmol/l

NT-proBNP, ng/L

Troponin T, ng/L

Patient demographics and baseline characteristics will be summarised by randomised treatment arm and overall using descriptive statistics (N, mean, standard deviation, median, 25/75 percentiles for continuous variables, and number and percentages of patients for categorical variables. There will be no statistical analysis of treatment difference. Any clinical important imbalance between the treatment groups will be noted.

5   Analysis

5.1   Outcome Definitions

5.1.1   Primary Outcome
Difference between CPAP treatment and usual care in change in AF burden (% of time in AF, as measured by loop recorder) from baseline (one month prior to randomization) to the *last three months of the intervention period*.

5.1.2   Secondary Outcomes

- Difference between CPAP treatment and usual care in change in AF burden (% of time in AF, as measured by loop recorder) from baseline (one month prior to randomization) to the *last month of the intervention period*.
- Difference between CPAP treatment and usual care in change in AF burden (% of time in AF, as measured by loop recorder) from baseline (one month prior to randomization) to the *last five months of the intervention period*.
- Difference between CPAP treatment and usual care in the proportion of patients with at least 25% reduction of AF burden (% of time in AF, as measured by loop recorder) from baseline (one month prior to randomization) to the *last three months of the intervention period*.
- Difference between CPAP treatment and usual care in change in AF symptom burden (assessed with the Atrial Fibrillation Severity Scale [AFSS] questionnaire) from baseline to five months after randomization:
  - AFSS Domain: frequency
  - AFSS Domain: duration
  - AFSS Domain: severity
  - AFSS AF burden
  - AFSS symptom score
  - AFSS Global well-being
- Difference between CPAP treatment and usual care in change in Quality of life (assessed with the Short Form-35 [SF-36] questionnaire) from baseline to five months after randomization:
  - SF-36 Component Summary: Physical
  - SF-36 Component Summary: Mental
- Difference between CPAP treatment and usual care in change in sleep quality and symptoms of OSA from baseline to five months after randomization:
  - Epworth Sleepiness Scale (ESS) sum score
  - Functional Outcomes of Sleep Questionnaire (FOSQ) sum score
  - Berlin Questionnaire sum score
  - Berlin Questionnaire sum score ≥ 2 (dichotomous)
  - Stop-Bang Questionnaire sum score
  - Stop-Bang Questionnaire sum score ≥ 3 (dichotomous)

5.1.3 Exploratory Outcomes

Difference between CPAP treatment and usual care in:

- Changes in cardiac structure and function (on echocardiography)
- Changes in cardiac biomarkers (troponin T and NT-proBNP)

- Changes in inflammatory and anti-inflammatory biomarkers in plasma and serum:
  - CRP, TNF-α, TNFRII, interleukin-6, interleukin-10, chemokines (MCP-1), endothelial function (von Willebrand), and metalloproteinases
- Changes in gene expression of white blood cells, and relationship with AF burden
- Activity patterns around the onset of PAF (assessed using Garmin Vivofit and activity recording)
- Change in body composition (on bioelectric impedance analysis)
- Lung function (spirometry)

5.1.4 Summary of Outcomes

Level	Outcome	Timeframe	Type
Primary	1. Change in AF burden	Baseline to last three months	Continuous
Secondary	2. Change in AF burden	Baseline to last month	Continuous
	3. Change in AF burden	Baseline to last five months	Continuous
	4. Proportion with more than 25% reduction in AF burden	Baseline to last three months	Dichotomous
	5. Change in AF symptoms (AFSS frequency)	Baseline to five months	Continuous
	6. Change in AF symptoms (AFSS duration)	Baseline to five months	Continuous
	7. Change in AF symptoms (AFSS severity)	Baseline to five months	Continuous
	8. Change in AF symptoms (AFSS AF burden)	Baseline to five months	Continuous
	9. Change in AF symptoms (AFSS AF symptom score)	Baseline to five months	Continuous
	10. Change in AF symptoms (AFSS AF global well-being)	Baseline to five months	Continuous

11. Change in quality of life (SF-36 physical component)	Baseline to five months	Continuous
12. Change in quality of life (SF-36 mental component)	Baseline to five months	Continuous
13. Change in sleep quality (ESS sum score)	Baseline to five months	Continuous
14. Change in sleep quality (FOSQ sum score)	Baseline to five months	Continuous
15. Change in symptoms of OSA (Berlin sum score)	Baseline to five months	Continuous
16. Symptoms of OSA (Berlin sum score ≥ 2)	Five months	Dichotomous
17. Change in symptoms of OSA (Stop-Bang sum score)	Baseline to five months	Continuous
18. Symptoms of OSA (Stop-Bang sum score ≥ 3)	Five months	Dichotomous

5.2 General Definitions and Derived Variables

5.2.1 Duration of atrial fibrillation

Duration of atrial fibrillation measured in hours and minutes will be converted to % of time in atrial fibrillation.

5.2.2 Body Mass Index

Body Mass Index (BMI) = Body weight in kilograms divided by the square of the height in meters.

5.2.3 Waist-hip ratio

Waist-hip ratio = The measured circumference of the waist divided by the measured circumference of the hip.

5.3 Analysis Methods

5.3.1 Primary Outcome

The primary outcome, difference between CPAP and usual care in change in AF burden from baseline to the last three months of the intervention period will be analysed with linear regression, with AF burden last three months as the dependent variable and treatment (CPAP vs usual care), study site (St Olavs University Hospital, Trondheim vs Rikshospitalet,

Oslo), and AF burden at baseline as explanatory variables. The mean difference between the two treatment groups with a 95% confidence interval will be reported, together with a P-value for the null hypothesis of no treatment difference.

The primary analysis will be done on the Full Analysis Set. A secondary analysis will be done on the Per Protocol Set.

5.3.2 Secondary Continuous Outcomes

All secondary continuous outcomes (see table in Section 5.1.4) will be analysed in the same manner as the primary outcome, with linear regression with the last measurement as the dependent variable and treatment, study site, and baseline measurement as explanatory variables. The results will be reported as the mean treatment difference with a 95% confidence interval, and P-value for the null hypothesis of no treatment difference.

All secondary continuous outcomes will be analysed on the Full Analysis Set.

5.3.3 Secondary Dichotomous Outcomes

The dichotomous outcomes will be analysed with Newcombe hybrid score 95% confidence intervals[2] for the difference between proportions and P-values for the Fisher mid-P test[2] of the null hypothesis of equal proportions.

The secondary dichotomous outcomes will be analysed on the Full Analysis Set.

5.3.4 Assumption Checks and Alternative Analyses

The assumption of normally distributed residuals in linear regression will be checked by plotting histograms of the residuals and examining their descriptive statistics, such as mean, median, standard deviation, and coefficient of skewness.

In cases where the distribution of the residuals is deemed to deviate too much from the normal distribution to allow linear regression to be used, a median regression (i.e. a quantile regression) will be performed instead of the linear regression. Then, the difference in medians (with a 95% confidence interval and a P-value for equality of medians) will be reported instead of the difference in means.

5.3.5 Missing Data

Missing data will be imputed such that the patient with missing data will have no change from baseline on the missing outcome. This can be considered a worst-case imputation strategy for the CPAP treatment.

5.3.6 Sensitivity Analyses

1. The primary outcome will be analysed on the Per Protocol Set.
2. Missing data will be imputed with the mean change in the respective treatment group. I.e., a patient in the CPAP group with missing data will be given a change for

the missing outcome equal to the mean change in the CPAP group, and vice versa for patients in the usual care group.

5.3.7 Subgroup Analyses

The primary outcome and the secondary outcomes AFSS AF burden (#8 in Section 5.1.4), AFSS symptom score (#9), SF-36 physical (#11), SF-36 mental (#12), ESS sum score (#13), and FOSQ sum score (#14) will be analysed in the following subgroups:

- Male vs females
- Age below median vs. age above median
- Duration of AF below median vs. duration of AF above median
- Left atrium size below median vs. left atrium size above median
- BMI below median vs. BMI above median
- Patients that use the CPAP mask for more than 4 hours a night vs. patients that use the CPAP mask for less than 4 hours a night (no change in the usual care group)
- Patients who either have a DC cardioversion or start treatment of Flecainide, Dronedarone, or Amiodarone after inclusion vs. patients who do not have a DC cardioversion or start treatment of either Flecainide, Dronedarone, or Amiodarone after inclusion.

A comparison of the effect of CPAP between the subgroups will be analysed by adding a subgroup indicator variable and an interaction term between the subgroup and treatment to the linear regression model. A significant subgroup effect will be declared if the interaction term is statistically significant at the 5% level. Within- and between subgroup effects will then be reported with mean differences and 95% confidence intervals.

6 Safety Analyses and Adverse Events

At each follow up visit all serious adverse events will be recorded in the Viedoc database with description of adverse event, with start and end date of the event. Information will be provided on the severity, causality and expectedness of the adverse event

Investigator records the maximum intensity of each AE using the levels mild, moderate, severe or life-threatening. Applicable treatment given and outcome of event will also be recorded

The summary of events will be exported from the Viedoc database. The summary of number of events will be used, rather than number of patients. Safety variables will be tabulated and presented for all patients in the safety set.

7   Statistical Software

Stata/SE 16.0 (StataCorp LLC, College Station, TX) will be used to perform the statistical analyses, except for the analyses of the dichotomous outcome, which will be done with Matlab R2014a (The MathWorks, Inc.).

8   References

1: Steven D, Rostock T, Lutomsky B, Klemm H, Servatius H, Drewitz I, et al. What is the real atrial fibrillation burden after catheter ablation of atrial fibrillation? A prospective rhythm analysis in pacemaker patients with continuous atrial monitoring. Eur Heart J 2008;29(8):1037-42, http://dx.doi.org/10.1093/eurheartj/ehn024.

2: Fagerland MW, Lydersen S, Laake P (2017). *Statistical Analysis of Contingency Tables*. Chapman & Hall/CRC, Boca Raton, FL.