

## Supplementary information

### **Rationale and Methodology of the SARAH Trial: Long-term cardiovascular outcomes in patients with resistant hypertension and obstructive sleep apnea**

**Running title: Rationale and methodology of the SARAH trial**

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## **1. Data Collection and study variables**

### **1.1. Baseline study variables**

1.1.1 Date of inclusion

1.1.2 Date of diagnosis of resistant hypertension (RH)

1.1.3 Sociodemographic variables: age and sex

1.1.4 Anthropometric Variables: weight, height, body mass index (BMI), neck circumference, waist circumference, and hip circumference. The current recommended waist circumference thresholds for abdominal obesity are > 102 cm in men and > 88 cm in women, with the exception of Asian and South American populations, for whom > 90 cm in men and > 80 cm in women are used<sup>1</sup>.

1.1.5 EuroQoL- 5D test and costs<sup>2</sup>.

1.1.6 Clinical Variables

a) Toxic habits:

a-1. Smoking habit: The number of cigars/cigarettes/pipes smoked and duration of smoking will be collected (for both current and former smokers). Current smoking is defined as an active daily smoking habit within the past month of any number of pipes or cigars/cigarettes.

a-2. Alcohol consumption: The consumption of 1 unit of alcohol an average of three times a week will be considered significant consumption.

b) Comorbidity (prior to inclusion in the study and the date of diagnosis):

b- 1. General comorbidity: Charlson index (adapted to age).

b- 2. Cardiovascular risk factor comorbidity:

b-2.1. Abnormal fasting glucose levels: glucose levels  $> 110$  mg/dl or  $\geq 126$  mg/dl without pharmacological treatment.

b-2.2. Diabetes mellitus: Medical diagnosis or treatment with anti-diabetic drugs or insulin.

b-2.3. Hypercholesterolemia: Medical diagnosis or treatment with statins or resins.

b-2.4. Hypertriglyceridemia: Medical diagnosis or treatment with fibrates.

b-2.5. Mixed dyslipidemia: Medical diagnosis or treatment with statins, resins, or fibrates.

c) Blood pressure (BP) variables:

c-1. Date of the diagnosis of hypertension (and date of the diagnosis of RH, if it is registered)

c-2. Office BP (the mean of the last 2 of 3 measurements with a 2-min lapse)

c-3. ABPM that allows RH to be diagnoses:

- Mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) (24 h).
- Mean SBP and DBP (day-time).
- Mean SBP and DBP (night-time).
- Maximum day-time SBD and DBP.
- Maximum night-time SBD and DBP.
- Minimum day-time SBD and DBP.
- Minimum night-time SBD and DBP.

d) Pharmacological treatment at the time of inclusion:

d-1. Number of drugs used to treat hypertension.

d-2. Agent group: Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers, beta blockers, diuretics, alpha receptor blockers, antialdosterones and others (dose and frequency).

d-3. Use of antialdosterone drugs (yes or no).

e) Therapeutic compliance:

e- 1. Morisky-Green test <sup>3</sup>.

e- 2. Haynes-Sackett test.

e-3. Optimal compliance based on pharmacy databases: Based on the electronic prescription record, optimal compliance is considered when the patient has picked up > 80% of the antihypertensive medications from the pharmacy within a predefined period (1 month for the inclusion visit and 1 year for the follow-up visits).

#### 1.1.7. Respiratory variables

- Epworth Sleepiness Scale score (ESS) (4)
- Type of sleep test: respiratory polygraph (RP) or polysomnography (PSG)
- Test date and location
- Apnea-Hypopnea index (AHI)
- Postural apnea-hypopnea index (in the supine position and non-supine position)
- % Supine
- % Obstructive and mixed events
- Number of apneas
- Apnea Index
- Number of hypopneas
- Hypopnea Index
- Total time in apnea/hypopnea
- Mean oxygen saturation (SaO<sub>2</sub>)

- Minimum oxygen saturation
- TC90 in minutes and percentage. TC90 is defined as the minutes or percentage of time with SaO<sub>2</sub> less than 90%
- Oxygen Desaturation Index (ODI) of at least 4% and 3%
- Obstructive sleep apnea (OSA) treatment:

Continuous positive airway pressure (CPAP) (yes or no)

Surgery (yes or no)

Mandibular advancement device (yes or no)

Date of treatment initiation

- When polysomnography is performed, the following additional data will be collected:

- General sleep parameters

Total sleep time (TST)

Sleep efficiency (total sleep time/time in bed)

Sleep latency

Rapid eye movement (REM) sleep latency

Wake after sleep onset (WASO) sleep stages

STAGE I: record time; % of TST

STAGE II: record time; % of TST

STAGE III: record time; % of TST

REM: record time; % of TST

- General analysis of leg movements

Total leg movements during sleep

Index of leg movements per h of sleep

- Arousals

Total number of arousals

Index of arousals per h of sleep

Index of arousals associated with leg movements

Index of arousals associated with respiratory events

Index of non-specific arousals

#### 1.1.8 Biochemical variables:

a) Biological parameters in the blood samples: (at baseline) hemoglobin, fasting plasma glucose, urea, calcium, creatinine, glomerular filtration rate (GFR), potassium, sodium, total cholesterol, triglycerides, high-density cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and uric acid levels.

#### 1.1.9 Asymptomatic organ damage variables:

##### - Heart:

a) Left ventricular hypertrophy (LVI): In echocardiography, left ventricular hypertrophy is defined as a posterior wall (PW) or septum  $> 11$  mm, or left ventricular mass (LVM) calculated according to the American Society of Echocardiography formula that is greater than  $115 \text{ g/m}^2$  in men and greater than  $95 \text{ g/m}^2$  in women.

b) Left atrial diameter enlargement in the echocardiogram (mm).

c) Atrial fibrillation: paroxysmal, permanent or persistent according to the electrocardiogram (EKG).

##### - Kidney:

a) Persistent microalbuminuria: defined as albuminuria of 20-300 mg/g creatinine in two urine samples collected at an interval of 6 months.

b) Proteinuria: defined as albuminuria greater than 300 mg in 24 h.

- Fundoscopy: Grade of hypertensive retinopathy according to the classification reported by Keith Wagener and Baker <sup>5</sup>.

- Peripheral arteriopathy: ankle-brachial index (ABI). An ankle-brachial index < 0.9 is considered low and has predictive value for cardiovascular events <sup>6</sup>.

- Carotid ultrasound: presence of a plaque.

#### 1.1.10 Biological samples

At the inclusion and follow-up visits, blood samples will be collected to obtain plasma, serum, buffy coat, and total blood for RNA extraction. Blood samples and data collected from them will be stored in the IRB Lleida Biobank.

### **1. 2. Follow-up variables**

#### 1.2.1 BP variables:

a) The home-measured blood pressure will be calculated at the medical visit. It is the mean of the last 4 measurements obtained at home (namely, 2 before breakfast and 2 before dinner whenever possible).

b) ABPM:

Mean SBP and DBP (24 h)

Mean SBP and DBP (day-time)

Mean SBP and DBP (night-time)

Maximum day-time SBD and DBP

Maximum night-time SBD and DBP

Minimum day-time SBD and DBP

Minimum night-time SBD and DBP

c) BP control will be defined as:

1. Optimal control: home BP < 140/90 mmHg or normal ABPM.
2. Uncontrolled: patients who do not meet the above criteria.

#### 1.2.2 Management:

- Number of drugs used to treat hypertension.
- Agent group: Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, beta blockers, alpha receptor blockers, antialdosterones and others (dose and frequency).
- Use of antialdosterone drugs (yes or no).

1.2.3 Anthropometric variables: weight, height, body mass index, abdominal fat, and neck, waist and hip circumferences.

#### 1.2.4 Compliance with CPAP in CPAP-treated patients with obstructive sleep apnea:

- a) Number of hours/night. Adherence to CPAP will be objectively assessed by reading the time counter of the device. If the average cumulative use is  $\geq 4$  h per night, the patient will be considered compliant.
- b) Tolerance (optimal, bad, intolerant)
- c) Type of mask
- d) Side effects and complications

#### 1.2.5 Biochemical and biological samples

#### 1.2.6 Costs

## 2. Study outcomes

The primary endpoint will be a composite of death from any cardiovascular cause, cardiac events (non-fatal myocardial infarction, hospitalization for unstable



angina, hospitalization for heart failure, and new onset atrial fibrillation), cerebrovascular events (non-fatal stroke and transient ischemic attack (TIA)), hypertensive crises and emergencies, peripheral arteriopathy or revascularization procedures,. All cardiovascular events will be independently evaluated by two physicians to establish a diagnosis. In cases with a disagreement, a third external physician will assess the case. The date of each event will be recorded.

## **2.1 Other endpoints**

The following secondary endpoints will be recorded:

- Kidney disease:

- Renal event: defined as the occurrence of renal insufficiency ( $\text{Ccr} < 60 \text{ ml/m}$ ) confirmed in two blood sample analyses collected at approximately 6-month intervals that is related to hypertensive nephroangiosclerosis.
- Persistent microalbuminuria: defined as albuminuria of 20-30 mg/g creatinine in two urine samples collected at an interval of 6 months.
- Proteinuria: defined as albuminuria greater than 300 mg in 24 h.

- Death from any cause.

All endpoints will be assessed at baseline and at each follow-up visit.

## References

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