Statistical Analysis Plan

INTERNATIONAL REGISTRY FOR AMBULATORY BLOOD PRESSURE AND ARTERIAL STIFFNESS TELEMONITORING

VASOTENS (**V**ascular health **AS**sessment **O**f **T**he hypert**ENS**ive patients) **Registry**

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In this document procedures for data collection and analysis are detailed.

1. INVESTIGATORS

An updated list of the Investigators, with their address and status will be periodically provided to Biotechmed by the Study Coordinator (Dr. Stefano Omboni) and saved on Biotechmed's server.
The study will start in each center only after official approval of the local Ethics Committee. The Investigator will received the BPLab device (if not yet owned) directly by BPLab. Upon confirmation of the study approval the Coordinator will inform BPLab which will ship the device to the Investigator (without the software).
The coordinator will inform Biotechmed that the center is ready to be opened and will give information on study address and Principal Investigator.
Biotechmed will prepare the sheet with the credentials and send them to the Investigator by e-mail: the e-mail will clearly state that before using the device for the first time the Investigator needs to contact Biotechmed which will help downloading e-THOLOMEUS and explain how to program the device, download the data from the device and fill in the e-CRF with the clinical information.
A group called "GRUPPO_VASOTENS 80000" will be created in the Tholomeus website and any Investigator will be named as 800 + its center code: e.g. 800 + 08 = 80008. The user's profile must be the same of ARTEMIS. Only "Cardiovascular diagnosis" (BPLab) and "CRF" modules must be activated.

2. DATA COLLECTION

Detailed study procedures and further information and details on the study are available in the study protocol.
Briefly, each center will enroll 100 patients from their pool of hypertensive patients. There are no specific inclusion criteria, except that:

- Patients must be at least 18 years-old
- Patients with frequent ectopic beats, including atrial fibrillation must be excluded
- Arm circumference must be at least 22 cm (appropriate cuff must be used in case of large arms)

Patients will be visited ideally at 6 month-intervals or once-a-year. During the visit they will be submitted to an ABPM and clinical data (see below) will be collected.

2.1 ABPM

The investigators must ensure that for any given patient and visit the ABPM is valid:

- Interval between measurement not less than 30 min
- At least 70% of expected readings
- At least 20 valid readings during the day
- At least 7 valid readings during the night

The device must always be programmed with clear indication of day-time and night-time starting time. Special period is not managed. The (surrogate) length of the aorta must be entered in the system at the time of programming the device, by measuring the distance between jugulum and symphysis.
If .BPW files are available they can be uploaded on the website. These files must contain the information on the length of the aorta.

2.2 CLINICAL DATA

That CRF must be completed with all the following information:

- Age
- Gender
- Height

- Weight
- Ethnicity
- Superficial distance between jugulum and symphysis (surrogate of aortic length) – see above
- Waist circumference
- Smoking status
- Alcohol drinking
- Coffee or tea drinking
- Dyslipidemia (yes/no and indication on treatment)
- Diabetes (yes/no and indication on treatment)
- Diagnosis of hypertension (yes/no and indication on treatment)
- Family history of premature CV disease
- Medical history, with particular regard to previous and/or concurrent CV diseases
- Office blood pressure and heart rate obtained in the same treatment condition as ABPM (only one value can be input: it could be the average of more values or just a spot measurement)
- Left ventricular mass index (LVMI) at echocardiogram
- When available, diameter of the ascending aorta assessed by the echocardiogram
- Intima-media thickness (IMT) at carotid ultrasonography
- ECG (indication on left ventricular hypertrophy, Sokolow–Lyon and Cornell index)
- When available, ankle-brachial index
- Microalbuminuria (as mg/24h) or albumin-creatinine ratio (as mg/g) and serum creatinine (estimated glomerular filtration rate – eGFR will be calculated by the software according to the Cockroft-Gault formula)
- When available, pulse wave velocity (PWV), augmentation index (AI) and central systolic blood pressure taken during the office visit with a validated device different from BPLab Vasotens (e.g. Sphygmocor or Complior)

Additionally, this information must be recorded at any visit:

- Drug treatments: explain that in case treatments are changed or replaced the Investigator must indicate dates and status. It is not necessary to add the drug again.
- Investigators must pay attention to record at any visit both new diseases and adverse events: the latter must be recorded in the "Events" section with start and end date and all the information needed to identify the event. Priority must be given to cardiovascular events, whereas other events must be placed under the label "Other" and a description must be entered.

3. ANALYSIS

The main analysis will assess:

- The general clinical characteristics of the population
- The relationship between BP and arterial stiffness and target organ damage / cardiovascular events
- The features of BP and arterial stiffness in presence of the metabolic syndrome

The following inclusion criteria will be considered:

- Male and female aged ≥18 years
- Good quality ABPM: i) at least 70% of the number of the expected readings over the 24 hours (discarded), ii) at least 20 valid measurements during the daytime and 7 during the nighttime

The parameters assessed will be:

- 24-hour average brachial SBP and DBP
- 24-hour average aortic SBP and DBP
- 24-hour average PWV
- 24-hour average aortic AI

- 24-hour wSD of SBP and DBP
- 24-hour ARV of SBP and DBP

Analysis will be done also for the day-time and night-time subperiods.
In each individual PWV will be normalized to a SBP of 100 mmHg and a HR of 60 bpm by a regression analysis of 24-hour PWV to 24-hour SBP and 24-hour HR. AI will be normalized to a HR of 75 bpm with the same procedure.
Statistical tests to be used will include analysis of variance (ANOVA) or covariance (ANCOVA) for continous variables with adjustments for confounding factors. Discrete variables will be analyzed by Chi-square test or logistic regression analysis. Survival analysis will be carried out by Kaplan-Meier plots, log rank test and Cox regression.

3.1 EVALUATION OF CLINICAL CHARACTERISTICS

Evaluation and comparison of the main study parameters for the following groups:

- Males vs. females
- Young (<65 years) vs. old (≥65 years)
- Age at risk: ≥55 years in males and age ≥65 years in females
- Ethnicity
- Smoking (smoker, no smoker, ex-smoker)
- Alcohol (yes vs. no)
- Coffee or tea (yes vs. no)
- Smoking or alcohol or coffee (yes vs. no)
- Family history for cardiovascular disease (yes vs. no)
- Previous cardiovascular diseases (yes vs. no)
- Any previous medical condition (yes vs. no)
- Arterial hypertension (untreated and treated)
- Antihypertensive treatment (yes vs. no)
- Dyslipidemia (untreated and treated)
- Lipid lowering treatment (yes vs. no)
- Diabetes (untreated and treated)
- Treatment of diabetes (yes vs. no)
- Metabolic syndrome (yes vs. no)
- Any cardiovascular disease (TIA, stroke, myocardial infarction, etc.) (yes vs. no)

Race will be modified according to the following rule in order to calculate ethnicity (missing values will be recoded into an appropriate value and if no category can be identified the “Caucasian” group will be assigned)

- Caucasian (1)
- Black (2)
- Asian (3)
- Hispanic (4)

In case of missing value for the following variables the missing value will be recoded to 0:

- Smoking
- Alcohol
- Coffee
- Left ventricular Hypertrophy at the ECG
- Family history for any CV disease
- Hypertension and therapy
- Number of antihypertensive drugs
- Dyslipidemia and therapy

- Diabetes and therapy
- Concomitant diseases and treatments
- Cardiovascular disease
- Cardiovascular risk
- Component of the metabolic syndrome and metabolic syndrome

3.2 EVALUATION OF TARGET ORGAN DAMAGE

3.2.1 CARDIAC DAMAGE

Cardiac damage will be based on LVMI, calculated as LVM divided by BSA, as follows [Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986;57:450-458]:

$$LVM = ((1.04 * ((((IVSD + PWD + LVEDD)^3) / 1000) - ((LVEDD^3) / 1000)) - 3.6) / ((WEIGHT^{0.425}) * (HEIGHT^{0.725}) * 0.007184))$$

Where:

IVSD = Interventricular septal thickness at end-diastole (mm)
PWD = Posterior wall thickness at end-diastole (mm)
LVEDD = LV end-diastolic dimension (mm)

Height is expressed in cm and weight in kg.

LVMI will recalculated from LVM.

Cardiac damage will be assessed according to ESH guidelines [Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F; Task Force Members. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2013 Jul;31(7):1281-357]:

- Males: LVMI > 115 g/m^2
- Females: LVMI > 95 g/m^2

An attempt will also be made to classify left ventricular hypertrophy according to ECG:

- Sokolow-Lyons index: SV1+RV5-6 >38 mm
- Cornell Index; S in V3 + R in aVL >24 mV in males and > 20 mV in females

3.2.2 VASCULAR DAMAGE

Carotid damage will be defined as thickening or plaque: Intima Media Tickness (IMT) in any district >0.9 mm. If available also a ankle-brachial index (ABI) <0.9 will be used for classification

3.2.3 RENAL DAMAGE

Renal damage will be defined according to:

- Estimated Glomerular Filtration Rate (GFR): <60 mL/min/1.73 m^2
- Urinary Albumin creatinine (UAC) ratio: ≥30 mg/g
- Microalbuminuria: ≥30 mg/24 hour

eGFR will be calculated according to the Cockroft-Gault formula [Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41]

- Male = [(140 - age) * (weight) * 1] / (72 * creatinine)
- Female = [(140 - age) * (weight) * 0,85] / (72 * creatinine)

3.2 EVALUATION OF THE METABOLIC SYNDROME

The metabolic syndrome will be evakluated according to the harmonized definition [Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC Jr; International Diabetes Federation Task Force on Epidemiology and Prevention; Hational Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009 Oct 20;120(16):1640-5]. Presence of 3 out of 5 of the following risk factors

a) Elevated waist circumference (Caucasian)

≥94 cm in males
≥80 cm in females

Elevated waist circumference (South America and Asia)

≥90 cm in males
≥80 cm in females

When waist circumference is missing a BMI ≥25 kg/m^2 will be used

b) Elevated triglycerides (≥150 mg/dL) or lipid-lowering treatment
c) Reduced HDL cholesterol (<40 mg/dL males and <50 mg/dL females) or lipid-lowering treatment
d) Elevated blood pressure (≥130 / 80 mmHg) or antihypertensive treatment
e) Elevated fasting glucose (≥100 mg/dL) or treatment for diabetes

In case of missing HDL it will be calculated in presence of total cholesterol, LDL cholesterol and triglycerides as

HDL = Total cholesterol – LDL cholesterol – Triglycerides /5

Also Cholesterol LDL and Triglycerides, if missing, will be recalculated starting from the available parameters.