TREAT

Multi-center Cross-sectional TReatment Evaluation of Apparent resistant hyperTension in Belgium

Study protocol

Scientific rationale

According to the WHO (2011), raised blood pressure is estimated to cause 7.5 million deaths, about 12.8% of the total of all annual deaths worldwide (1). Hypertension can be effectively treated with lifestyle changes and medication. Lowering elevated blood pressure reduces the risk of major cardiovascular events (2). The first step for achieving blood pressure reduction are lifestyle changes such as losing weight, decreasing sodium intake, increasing physical activity, and adopting a healthy diet. These measures can significantly decrease the risk of health complications associated with hypertension (3) In cases where lifestyle changes alone are not sufficient, medication is used. Several classes of medications, collectively referred to as antihypertensive medications, are available for treating hypertension. However, despite the established efficacy of antihypertensive treatments, among treated hypertensive patients there lies a cohort at the upper end of the cardiovascular risk spectrum; that is, patients whose hypertension is resistant to treatment.

Hypertension is defined as resistant to treatment when the recommended treatment strategy fails to lower office SBP and DBP values to <140 mmHg and/or <90 mmHg, respectively, and the inadequate control of BP is confirmed by ABPM or HBPM in patients whose adherence to therapy has been confirmed. The recommended treatment strategy should include appropriate lifestyle measures and treatment with optimal or best-tolerated doses of three or more drugs, which should include a diuretic, typically an ACE inhibitor or an ARB, and a CCB (4). Pseudo-resistant hypertension and secondary causes of hypertension should also have been excluded. According to the ESC/ESH guidelines on hypertension management the main causes of pseudo-resistant hypertension are:

- **Poor adherence to prescribed medicines**: frequent cause of pseudo-resistant hypertension, occurring in ≤50% of patients assessed by therapeutic drug monitoring, and is directly related to the number of tablets prescribed
- **White-coat phenomenon:** elevated office BP, but BP is controlled at ABPM or HBPM. This phenomenon is not uncommon in these patients, hence the recommendation to confirm office hypertension with ABPM or HBPM before confirming the diagnosis of resistant hypertension.
- **Poor office BP measurement technique**: usually the use of cuffs that are too small relative to the arm circumference
- **Marked brachial artery calcification**: especially in older patients with heavily calcified arteries.
- **Clinician inertia:** inadequate dosing or irrational combinations of BP-lowering drug therapies

Prevalence studies of resistant hypertension have been limited by variation in the definition used, and reported prevalence rates range from 5–30% in patients with treated hypertension (4). When the above mentioned pseudo-resistance issues have not yet been ruled out as a potential cause for the ongoing high BP, the term apparent treatment-resistant hypertension (aTRH) is used. Apparent TRH can be considered as an overdiagnosis (5). After applying a strict definition and having excluded causes of pseudo-resistant hypertension, the true prevalence of treatment resistant hypertension (TRH) is likely to be <10% of treated patients. Patients with resistant hypertension are at higher risk of Hypertension Mediated target Organ Damage (HMOD), Chronic Kidney Disease (CKD), and premature CV events. Therefor a correct diagnosis of TRH is of utmost importance to identify these

high risk patient and offer them an adequate treatment. Furthermore a correct diagnosis of RHT is also of utmost importance to identify these patients with aRHT to avoid irrational overtreatment of these patients.

In Belgium no data exists on the prevalence of apparent and true resistant hypertension. Many patients may be referred to specialized services for resistant hypertension while having aRHT. To evaluate the extent of this overdiagnosis phenomenon in Belgium we will conduct a cross-sectional study of the prevalence of TRH in patients referred to specialized hospital centers for "resistant hypertension", using the correct ESC/ESH definition, and with consideration of individual patient morbidity, and the three assessable key aspects of pseudo-resistance — White Coat Hypertension, Inadequate dosing or irrational combinations of BP-lowering drug therapies, and non-adherence.

2. Objectives

To evaluate in daily clinical practice in Belgium and the extent of pseudo-resistant and true resistant hypertension in patients referred to specialized hospital centers for apparent resistant hypertension.

Expected added value

This study will allow us to:
- gain insight in the prevalence of true resistant hypertension and pseudo-resistant hypertension within a population of apparent resistant hypertensive patients in Belgium.
- identify the main contributors of pseudo-resistant hypertension (white coat hypertension, inadequate dosing & irrational combinations of BP lowering drugs, of non-adherence to treatment
- identify the treatment type and patient type of patients with apparent resistant hypertension, pseudo-resistant hypertension and true resistant hypertension
- to make recommendations how to avoid overdiagnosis of pseudo-resistant hypertension

3. Design and Methods

TREAT is a single-visit, multicentric, non-interventional, cross-sectional survey of patients referred to specialized hospital centers for apparent resistant hypertension.

The study design has the following characteristics:

- Only existing data that is registered in specialized hospital centers daily practice will be collected. These routine data are not specifically collected to achieve the purpose of the study. In Belgium specialized hypertension hospital centers adopt the ESC/ESH guidelines for hypertension management.
- The data is collected at one specific moment in time, so that we get a cross-sectional overview of the population studied. The study is hence limited to the current situation (in 2020).
- The study is a purely descriptive study (the statistical analysis can describe the current situation). The development of this situation over time is not investigated (this is only possible with a longitudinal study).

This study methodology allows to answer perfectly to the research questions.

No specific investigations or therapies will be prescribed as part of this survey, aside from answering the Hill Bone questionnaire if deemed useful by the treating physician and so patient care will not be influenced.

This study uses the Hill Bone Scale instrument to assess Adherence to the treatment.
This **9-item** scale has broad application across various chronic diseases and conditions for self-assessment of medication adherence. It is a useful tool for conditions like hypertension, diabetes, COPD, and stroke.
These brief scales provide a simple method for clinicians in various settings to assess patients' self-reported adherence and to plan appropriate interventions. Each can be self-administered or interviewer-administered in less than 5 minutes, thus making each clinically useful.
The Hill Bone scale is proposed to the treating physician, without the obligation of use, to assess therapeutic adherence to blood pressure lowering treatments.

The Hill-Bone scale consists of 9 four-point Likert-type items (1 = *none of time*, 2 = *some of the time*, 3 = *most of time*, and 4 = *all the time*). The total scores on this subscale range from 9 to 36 with higher scores reflecting poorer adherence to antihypertensive drug therapy.

This study, based on available data and requiring no input from the patients concerned, aside from answering the Hill Bone questionnaire if deemed useful by the treating physician, is considered retrospective within the scope of section 1.4 of the May 2008 guidelines on non-interventional studies (6). The Human Experiment Act (7 May 2004) is therefore not applicable. In this context, the methodology is in line with the recommendations on non-interventional studies detailed in the Pharma.be Deontological Code (March 27, 2019) and the May 2008 guidelines on non-interventional studies (6,7).

4. Patients and investigators

The number of patients, for which data will be collected, is estimated at 390. This number is not based on statistical calculations – which is inherent to the used study design – but in accordance with the usual sample size for this type of epidemiological research in Belgium (ie. ± 10% of recent epidemiological hypertension studies)

4.1 Patient inclusion criteria

- Age ≥18 years
- Referred to specialized hospital centre for apparent resistant (non-controlled) hypertension
- SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg
- Treated with ≥ 3 antihypertensive molecules

4.2 Patient exclusion criteria

- Patients referred to specialized hospital centre with suspicion of secondary hypertension

4.3 Investigators

Investigators are specialist physicians working hospital centers in Belgium, who manage patients with apparent resistant hypertension

The number of doctors to collect data from 390 patients is estimated at 39 specialists. Each specialist collects data from 10 patients seen at his clinical practice who respond to the inclusion criteria. These general practitioners are recruited over the entire geographical region of Belgium, ensuring a balanced geographical spread, in a period of 3 months (March 2020 to June 2020). This allows the collaborators of Servier Benelux to make an appointment with the investigators in order to ask agreement on participation, signing of the contract and deliver the study forms.

To avoid selection bias, the specialist physicians are asked to include the last 10 consecutive patients seen in their clinical practice who respond to the inclusion criteria. The investigator needs to inform the patient about the use of data from his/her patient files in a non-interventional retrospective study.

5. Data collection

The data is collected according to the patient's medical records. No future observations are planned with the patients during future contacts with the specialist physician (consultation).
In Belgium, diagnosis of resistant hypertension according to the ESC/ESH guidelines is based on:

- The patient's history, including lifestyle characteristics, alcohol and dietary sodium intake, interfering drugs or substances, and sleep history
- The nature and dosing of the antihypertensive treatment.
- A physical examination, with a particular focus on determining the presence of HMOD and signs of secondary hypertension.
- Confirmation of treatment resistance by out-of-office BP measurements (i.e. ABPM or HBPM).
- Laboratory tests to detect electrolyte abnormalities (hypokalemia), associated risk factors (diabetes), organ damage (advanced renal dysfunction), and secondary hypertension.
- Confirmation of adherence to BP-lowering therapy

For each eligible patient, the investigator records the following existing data on an observation form:

- Number of the patient in the study (1 to 10),
- Age, sex, height, weight and heart rate
- Number of years actively treated for high blood pressure
- co-morbidities (diabetes, prior CV events, chronic kidney disease, heart failure, dyslipidemia)
- Office systolic/diastolic blood pressure (mmHg)
- ABPM or HBPM systolic/diastolic values (mmHg) : measured according to the methodology described in the ESC/ESH 2018 Guidelines for the management of hypertension, if available
- antihypertensive treatment upon referral to hospital (pill burden, number of antihypertensive molecules, INN, brand name, therapeutic class and daily dose)
- self-reported adherence to antihypertensive treatment

Beside the patient data, the observation form contains the investigators name, address, signature and stamp, in order to contact the physician if needed and to guarantee authenticity

The observation form contains the contact information of the responsible person for the study at Servier Benelux, in order to allow investigators to receive additional information if needed

Once an investigator agrees to participate to the study, the data will be collected by the investigator in a period of 3 months after consent of the investigator concerning participation in the study. This period allows the general practitioners to identify 10 patients eligible for the study and to fill in the case report form. After this period, the collaborators of Servier Benelux have 2 months to gather the case report forms. As the last inclusion for recruitment of participating specialist physicians is May 2020, all data should be available for analysis after October 2020, which is the end date of this study. Data collected in this cross-sectional survey is property of Servier Benelux. Publication of data gathered during this survey is only possible after permission of Servier Benelux.

6. Pharmacovigilance

6.1. DEFINITIONS

6.1.1. Pharmacovigilance information

Pharmacovigilance data include any unintended or adverse event associated with the use of a medicinal product in humans, whether or not considered drug related, including the following special situations (situations where no adverse event occurred but information needs to be collected):
- exposure during pregnancy or breastfeeding,
- overdose, abuse, misuse, off label uses, medication error, occupational exposure,
- lack of efficacy
- unintended benefit
- transmission of an infectious agent

6.1.2. Adverse Event (AE)

Adverse event (synonym adverse experience): any untoward medical occurrence in a patient or a clinical-trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

*6.*1.3. Adverse (drug) reaction (ADR)

Adverse reaction (synonyms: Adverse drug reaction, Suspected adverse (drug) reaction, Adverse effect, Undesirable effect: a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

6.1.4. Serious adverse (drug) reaction (SADR)

Serious adverse reaction: an adverse reaction which results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect. Life threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe. Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

6.2. RESPONSIBILITIES

If during the course of this study the physician detects unreported adverse events, adverse drug reactions or special situations associated with any Servier product while going through the patients' medical files or is informed of such events by the patient, he should report this as soon as possible using the Adverse Drug Reaction Form. This Form must be sent to the responsible for Pharmacovigilance at Servier Benelux, dr. Xavier Pottier (fax: 02/529.43.89, e-mail: pharmacovigilance.be@servier.com, tel: 02/529.43.11). If needed, the responsible person for Pharmacovigilance of Servier Benelux may contact the physician to obtain additional information.

7. Analysis of data

After quality control, the data of all properly filled out case report forms is entered into an Excel table to perform the following descriptive statistical analysis:

- prevalence of true resistant hypertension and pseudo resistant hypertension within a population of apparent resistant hypertension patients
- characteristics of the population with apparent resistant hypertension, true resistant hypertension and pseudo resistant hypertension.
- Medication of patients with apparent resistant hypertension, true resistant hypertension and pseudo resistant hypertension (pill burden, number of antihypertensive molecules used, type of combinations used, dosage of different antihypertensive classes used)
- Prevalence of white coat hypertension as contributor for pseudo resistant hypertension
- Evaluation of therapeutic adherence as contributor for pseudo resistant hypertension
- Evaluation of , inadequate dosing & irrational combinations of BP lowering drugs as contributor for pseudo resistant hypertension

8. Study report and publication

After analysis of the data and interpretation of the results, a study report is prepared and approved by the Medical Affairs department of Servier Benelux. Presentation of the results as abstracts at (inter)national scientific congresses and publication in a scientific journal is planned.

The scientific report (or scientific publication) will be sent to all investigators who participated in the study and will also be kept at the disposal of the bodies of pharma.be as referred to under Article 52, § 1 of the Deontological Code of 27 March 2019 and will be submitted following a request on their part

9. Quality control

The study protocol has been drawn up in collaboration with the Medical Affairs department of Servier Benelux, which has approved it and oversees the good course of the study.

The methodology of this cross-sectional survey is in line with pharma.be deontological Code of 27 March 2019 and the May 2008 guidelines on non-interventional studies

To check the quality of the collected data, quality control takes place taking into account the quality risks inherent to the methodology of this observational study. For this purpose, the Medical Affairs Department of Servier Benelux will perform a quality control on a sample of 5% of the collected case report forms.

The Medical Affairs department of Servier Benelux manages the data, performs statistical analysis and prepares the study report.

The role of the medical representatives of the Servier Group remains limited to the following two actions:

- opening visit: presentation of the study, submission of the protocol and case report form, signing of the contract with the investigator
- closing visit: collection of the completed case report forms

10. References

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5. Carter SM, Rogers W, Heath I, et al. The challenge of overdiagnosis begins with its definition. BMJ 2015; DOI: 10.1136/bmj.h869
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7. Pharma.be code of deontology 27 March 2019

11. Signatures

Investigator	**Servier Benelux**
Name:	Name: Van Nieuwenhuyse Bregt
Signature:	Signature: 


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