STUDY PROTOCOL

ADHERENCE TO ANTIHYPERTENSIVE THERAPY: ANALYSIS OF INITIATION, IMPLEMENTATION, DISCONTINUATION AND POSSIBLE RISK FACTORS IN PORTUGUESE PRIMARY CARE UNITS

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STUDY INFORMATION

Title	Adherence to antihypertensive therapy: analysis of initiation, implementation, discontinuation and possible risk factors in Portuguese primary care units
Study Reference Number	ENCEPP/SDPP/7757
Substance class	C02: C02A; C02C; C02D; C02K. C03: C03A; C03B; C03C; C03D; C03E. C07: C07A. C08: C08C; C08D; C08G. C09: C09A; C09B; C09C; C09D.
Objectives	The main objective of the study is to determine adherence to antihypertensive therapy in newly treated hypertensive patients in primary care units from Region of Lisbon and Tagus Valley. The secondary objective is to identify risk factors for non-adherence.
Country of study	Portugal
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1. RESPONSIBLE PARTIES

Study conduct: CEDOC - Chronic Diseases Research Centre of the Faculdade de Ciências Médicas da Universidade Nova de Lisboa

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2. LIST OF ABBREVIATIONS

ARSLVT	Administração Regional de Saúde de Lisboa e Vale do Tejo (Regional Health Administration of Lisbon and Tagus Valley)
ATC	Anatomical Therapeutic Chemical
CI	Confidence Intervals
CV	Cardiovascular disease
DDD	Defined Daily Dose
ICPC	International Classification of Primary Care
INE	Instituto Nacional de Estatística (Statistics Portugal)
NHS	National Health Service
PDD	Prescribed Daily Dose
RRP	Recommended Retail Price
SIARS	Sistema de Informação da ARSLVT (Information System of ARSLVT)

3. ABSTRACT

TITLE: Adherence to antihypertensive therapy: analysis of initiation, implementation, discontinuation and possible risk factors in Portuguese primary care units

RATIONALE AND BACKGROUND: Non-adherence to antihypertensive therapy is an important component of preventable cardiovascular morbidity and mortality, mostly relevant in the case of a recent diagnosis or prescription of new antihypertensive drugs. It has been estimated that up to 30% of patients fail to initiate prescribed therapy and that during the first year of treatment up to 50% of patients discontinue their therapy.

OBJECTIVES: The main objective of the study is to determine adherence to antihypertensive therapy in newly treated hypertensive patients in primary care units from Region of Lisbon and Tagus Valley. The secondary objective is to identify risk factors for non-adherence.

METHODS: We will conduct an observational retrospective cohort study. The study population is formed by all newly diagnosed and treated hypertensive patients in the primary care units of Region of Lisbon and Tagus Valley during the first trimester of 2011. Prescription and claims data will be collected from SIARS for each patient during a follow-up of 2 years after index date and a run-in period of 6 months. Initiation is determined by picking-up the first prescription in a pharmacy within a 180-day period. Implementation of therapy is measured with Medication Possession Ratio and persistence, as a measure of the duration of time from initiation to discontinuation is determined by refill persistence according to a maximum allowed treatment gap of 90 days. This allows us to separate the population in two cohorts: adherents and non-adherents. Differences between the two groups will be handled by logistic regression.

DISCUSSION: Little is known in Portugal about adherence to antihypertensive therapy, especially at a population level. To our best knowledge this will be the first study in the country to measure medication adherence with prescription and claims data. Data emerging from this study will hopefully allow a framework to identify patients at risk for non-adherence is its different manifestations and develop strategies to reduce that risk.

KEY-WORDS: Adherence to antihypertensive therapy; initiation, implementation and discontinuation.

4. MILESTONES

MILESTONE	PLANNED DATE	ACTUAL DATE
Registration in the EU PAS register	14/11/2014	
Start of data collection	15/12/2014	
End of data collection	31/12/2014	
Start of data analysis	01/01/2015	
Final report of study results	30/09/2015	

5. RATIONALE AND BACKGROUND

Cardiovascular disease (CVD) is the main cause of premature death in industrialised countries and is also a major cause of morbidity worldwide, as well in Portugal[1-2] where it's responsible for up to 32% of all deaths[3]. Hypertension is a relatively common chronic disease and one of the major risk factors for CVD[1-6]. It has been estimated that overall, 42.1% of the Portuguese adult population aged 18 to 90 years, would have hypertension[2].

The relationship between high blood pressure and risk of CVD is continuous, consistent and independent of other risk factors[1,4,7]. During the last decades, the benefits of antihypertensive drugs in reducing the risk of major cardiovascular events have been extensively demonstrated[3-5,7-8].

However, the control of hypertension continues to be inadequate despite the excellent array of effective, well-tolerated medications[4]. In Portugal, among hypertensive subjects, only 46.1% are aware of their high blood pressure, 39% actually take antihypertensive medication and only 11.2% have their blood pressure controlled[2].

The precise reasons for patients not achieving target blood pressure despite being treated are not completely clear yet, but one major (and modifiable) reason is the fact that patients often do not only fail to take their medication as has been prescribed by their physician, e.g. non-adherence, but also fail to use it for a long uninterrupted period of time, e.g. non-persistence[9,10].

Non-adherence and/or non-persistence are an important component of preventable cardiovascular morbidity and mortality. High-adherent patients have a lower risk of major cardiovascular events, hospital admissions and global health care costs[11-13]. The consequences of poor adherence and persistence with antihypertensive therapy are the same as those for hypertension itself[14]. It's known that non-adherence may also lead to unnecessary adjustments of drug regimens[15].

Literature has shown that a substantially poorer medication adherence rate is observed when using a new prescription cohort[4,7,8], and accounting for those who fail to initiate the new medication, e.g. primary non-adherence, fail to ever refill, e.g. early discontinuation, and time after discontinuation, rather than the more commonplace approach of only observing ongoing users[5,16-17]. Conventional adherence measures therefore systematically underestimate the public health burden of poor medication adherence of newly prescribed medications[7].

A new taxonomy for describing and defining adherence to medications defines it as the process by which patients takes their medications as prescribed. Adherence has three components: initiation, implementation and discontinuation. The most fundamental point in this novel approach is that adherence is not a therapeutic parameter that can be described by a single number, as usually reported in the literature[18].

To our knowledge, this will be the first study to describe adherence to antihypertensive drugs as a process, evaluating all components:

1. Initiation of the treatment or primary adherence
    a. Early discontinuation
2. Implementation of the dosing regimen
3. Discontinuation

5.1. LOCAL CONTEXT

In Portugal, healthcare is provided by two overlapping systems: a publicly funded National Health Service (NHS) and voluntary private and public health insurance. The NHS has universal coverage, and 20% of the population has additional insurance coverage[19]. In spite of that, the costs with reimbursement of drugs of voluntary private and public health insurance in Portugal has been decreasing over the last years, representing in 2011, less than 12.5% of the NHS total costs with reimbursement of medicines[20].

Electronic prescribing is mandatory for all NHS reimbursed drugs regardless the health care providing system (public sector, i.e. primary heath care centres and NHS hospitals and private sector) since 2010[21]. A report from the Portuguese Ministry of Health (February 2011 to June 2012) shows 98.7% of electronic ambulatory prescriptions in the primary health care sector; 97.7% in public hospitals and 73.7% in private practice[22].

Prescriptions for medicines must include the International Non-proprietary Name of the active substance, its pharmaceutical form, the strength, the presentation (package size) and the dosage regimen. All prescription information is collected centrally by NHS[23]. However, since the inclusion of the dosage regimen is not mandatory for prescription validation, that specific information is not registered centrally but only on the electronic medical record of the patient.

For acute situations, medical prescriptions are valid for a 30-day period after the date of prescription - single prescription with a maximum of two packages per drug. For chronic conditions, the prescription can be renewed up to three times – three identical prescriptions with a maximum of two packages per drug to be dispensed within six months after the date of the prescription.

Community pharmacies then submit electronic claims for reimbursement of the government funded components of dispensed drugs to a centralized reimbursement system. For antihypertensive drugs, the NHS pays 69% of the reference price of the homogeneous group when applicable or 69% of the Recommended Retail Price (RRP) when the drug is not included in a homogeneous group.

Prescription and dispensing/claims data can be linked in SIARS, which is an administrative database that allows the linkage through prescription number and/or patient's NHS number. This repository covers over 3.5 million inhabitants in the region of Lisbon and Tagus Valley.

6. OBJECTIVES

The main objective of the study is to determine adherence to antihypertensive therapy in newly treated hypertensive patients in primary care units from Region of Lisbon and Tagus Valley.

SPECIFIC OBJECTIVES (PRIMARY):

- Determine initiation or primary adherence to antihypertensive therapy;
- Determine the implementation of antihypertensive therapy in the observation period;
- Determine persistence at 1 year and 2 years.

SPECIFIC AIMS (SECONDARY):

- Identify risk factors for primary non-adherence to antihypertensive therapy;
- Identify risk factors to poor quality of implementation of antihypertensive therapy;
- Identify risk factors for discontinuation of antihypertensive therapy;

7. RESEARCH METHODS

7.1. STUDY DESIGN

We will conduct an observational study, more specifically a retrospective cohort study. We will use a new prescription cohort of hypertensive patients. The new prescription cohort will allow us to determine the first step of adherence, e.g. initiation as well early discontinuation.

For that purpose, prescription and claims data of antihypertensive drugs will be collected for every participant for a 2-year follow-up period after index date. We assume that a follow-up period of 2 years is sufficient for patients to establish a utilization pattern and includes a sufficient number of claims data to generate stable adherence estimates during ongoing use. Additionally, it reduces the limitation of just 1-year follow-up mentioned in other publications[11;24-27].

This first cohort, once the primary objective is achieved, will be divided in an adherent group and a non-adherent group and their differences will be analysed.

Hypertension will be defined in the terms of codes K86 and K87 of the International Classification of Primary Care - ICPC, 2nd ed. using the Portuguese translation[28].

In terms of medication, the ATC codes analysed will be:

- C02: antihypertensives
    i. C02A: antiadrenergic agents, centrally acting
    ii. C02C: antiadrenergic agents, peripherally acting
    iii. C02D: arteriolar smooth muscle, agents acting on

iv. C02K: other antihypertensives

- C03: Diuretics
  i. C03A: low-ceiling diuretics, thiazides
  ii. C03B: low-ceiling diuretics, excl. thiazides
  iii. C03C: high- ceiling diuretics
  iv. C03D: potassium-sparing agents
  v. C03E: diuretics and potassium-sparing agents in combination
- C07: Beta blocking agents
  i. C07A: beta blocking agents
- C08: Calcium channel blockers
  i. C08C: selective calcium channel blockers with mainly vascular effects
  ii. C08D: selective calcium channel blockers with direct cardiac effects
  iii. C08G: calcium channel blockers and diuretics
- C09: Agents acting on the renin-angiotensin system
  i. C09A: ACE inhibitors, plain
  ii. C09B: ACE inhibitors, combinations
  iii. C09C: angiotensin II antagonists, plains
  iv. C09D: angiotensin II antagonists, combinations.

This will be an exploratory study because to our best knowledge this is the first study in Portugal measuring medication adherence with prescription and claims data.

7.2. SETTING AND POPULATION

Study population consists of all newly diagnosed and treated adults patients with hypertension in the primary care units of Region of Lisbon and Tagus Valley from January 1st to March 31st 2011 who used no antihypertensive drugs prior to January 1st 2011.

Patients will enter the cohort from index prescription on, in order to allow determining initiation. For those who initiate therapy, the date of the first acquisition of an antihypertensive drug at a community pharmacy is the index date. After that, patients will be followed-up for a 2-year period (730 days). This will be looked at retrospectively.

To determine whether patients are truly new users of antihypertensive therapy, a period of data collection before initiation of antihypertensive therapy is required. Patients could have been diagnosed and received prescriptions within that period by other providers, including specialist and hospital outpatient settings. In Portugal, under the NHS the majority of hypertensive patients consult their general practitioner to renew their prescriptions[6].

Therefore prescription and claims data will be collected additionally for a period of 6 months prior to January 1st 2011. This 6-month run-in period is recommended by Halpern[29] and was also used in other studies[11,26,27,30,31].

Patients with no prescriptions and/or no claims for any antihypertensive drugs in the 6-month period before the index prescription are classified as newly treated (new users) patients, whereas those who received antihypertensive drugs prescriptions in this 6-month period are classified as established patients and will be censored.

7.3. VARIABLES

EXPOSURE DEFINITIONS:

Exposure to antihypertensive therapy is defined as the duration of a dispensing of any prescription for any antihypertensive drug within the observation period, starting from INITIATION and ending at DISCONTINUATION or the end of the observation period, whichever occurs first.

INITIATION (or PRIMARY ADHERENCE) is the length of time from index prescription to filling-up that prescription in a community pharmacy within a 180 days period, which is the maximum allowed period of time for acquisition of a prescribed medicine in a community pharmacy in Portugal. In opposition, primary non-adherence is defined as a failure to have index prescription dispensed (not filled up at the pharmacy) within a 180 days period,

IMPLEMENTATION is the extent to which a patient's actual dosing regimen corresponds to the prescribed dosing regimen, from initiation until discontinuation.

To determine implementation, we must consider the number of days' supply obtained in each prescription, e.g. the duration of a prescription. Since SIARS do not include information about the recommended or individual dosage regimen, the theoretical duration of a prescription will be calculated by multiplying the prescribed daily dose (PDD) by the number of units per package. For this study, we decide not to use the defined daily doses (DDD), since DDD does not necessarily reflect the recommended or PDD in antihypertensive class drugs[32]. The PDD will be estimated by considering the average daily dose for each antihypertensive drug related to hypertension.

DISCONTINUATION: marks the end of therapy, allowing the estimation of PERSISTENCE, which is the length of time from initiation (index date) to discontinuation of therapy.

A sub-topic of discontinuation is EARLY DISCONTINUATION is the fail to ever refill. In this case, a patient would fill up only the index prescription.

VARIABLES FOR PATIENT CHARACTERIZATION (AS EXTRACTED FROM SIARS)**:**

1. Age: continuous (years)
2. Gender: male/female
3. ICPC, 2nd ed. diagnoses: K86/K87
4. Date of diagnoses
5. Affiliation with the primary care unit:
    a. Primary enrolment in the unit
    b. Transferred from another unit
    c. Not enrolled with the unit
6. Housing parish code (according to INE)

VARIABLES FOR PRESCRIBER CHARACTERIZATION:

1. Primary care unit unit
2. Primary care physician assigned to the patient: yes/no

VARIABLES FOR PRESCRIPTION CHARACTERIZATION:

1. Type of prescription:
    a. single prescription: up to two packages to be dispensed within 30 days;
    b. triple prescription: up to two packages each to be dispensed within 6 months.
2. Date of prescription
3. Antihypertensive drugs prescribed (data per drug):
    a. ATC Code
    b. Brand name
    c. Generic name
    d. Dosage
    e. Amount of units per package
    f. Number of packages prescribed
    g. RRP
    h. Reimbursement cost for NHS
    i. Out-of-pocket cost for patient
4. Antihypertensive drugs dispensed (data per drug):
    a. Dispensing date
    b. ATC Code
    c. Brand name
    d. Generic game
    e. Dosage
    f. Amount of units per package
    g. Number of packages dispensed
    j. RRP

k. Reimbursement cost for NHS
l. Out-of-pocket cost for patient

7.4. DATA SOURCES

Data will be collected for the period between June 1st 2010 and June 30th 2013 from SIARS, which is an administrative database that allows linkage between prescription and claims data through prescription number and/or patient's NHS number. This repository covers over 3.5 million inhabitants in the region of Lisbon and Tagus Valley. All reimbursed medicines are registered in the claims data. Data will be collected and provided to the research time by employees of ARSLVT, according to defined specifications in a variables codebook. Therefore, researchers will not be directly involved in data collection.

Electronic prescribing gives the research team the possibility to identify this new prescription cohort and determine whether medication was ever dispensed (initiation or primary adherence), was refilled at least once (early persistence), used as prescribed (implementation), or subsequently discontinued.

DATA PERMIT PROCESS:

This protocol has been approved by the ethics committee of ARSLVT – protocol number 119/CES/INV2013 - and it's under approval by the ethics committee of NOVA Medical School.

7.5. STUDY SIZE

The study population will be formed by all newly diagnosed and treated hypertensive patients in the primary care units of Region of Lisbon and Tagus Valley during the first trimester of 2011. We estimate a study size of more than 20.000 members.

7.6. DATA ANALYSIS PLAN

We will start by pre-processing raw data provided by ARSLVT in order to check for incomplete data, errors or outliers and discrepancies.

The application of exclusion criteria will censor all patients who don't comply with inclusion criteria set in advance.

From that, we'll move on to fill in the database with:

- PDD for each prescription;
- Theoretical duration and end date of the prescription;
- Time to initiation;
- Medication Possession Ratio (MPR);

- Gap between prescriptions within the same ACT code or in cases of switching (expressed in days and in proportion of the duration of the prescription after which the treatment gap occurs);
- Time to discontinuation;

This data allow the characterization of patients concerning to the study outcomes: initiation, implementation and discontinuation.

For baseline description, all patients with index diagnoses and index prescription from January 1st to March 31st 2011 will be included.

All continuous variables will be described using standard statistical measures: number of observations, mean, standard deviation, median, 1st and 3rd quartile, minimum and maximum. All categorical variables will be summarized with absolute and relative frequencies.

ADHERENCE MEASURES:

Initiation is a time-to-event variable with a well-defined time origin (index prescription) and an end-point which is the acquisition of index prescription. This end-point will be used as a proxy for first dose taken. It will be quantified as the proportion of patients not exceeding a 180-day period after index prescription and will be analysed and interpreted using standard survival analysis.

A patient who initiates treatment will be classified as a new user; a patient with primary non-adherence will be classified as a non-user.

Implementation will be quantified by estimation of MPR, which is a measure of medication availability widely used in long-term medication, such as antihypertensive medication[9,33-35]. It reports medication availability by estimating the proportion of days' supply obtained from community pharmacies during a specified observation period and it will expressed by:

$$MPR = \frac{\text{number of days supply obtained during observation period}}{\text{number of days in observation period}} \text{ x } 100$$

where the observation period refers to the period from index date to 730 days afterwards with the prior 6 months of extracted prescribing and dispensing data forming a run-in period for the analysis. The time between any one dispensing and the subsequent dispensing is known as the refill interval.

The end date of a prescription equals the start date plus the duration of the prescription. In case of overlapping prescriptions, the second prescription is shifted forward to account for drug stockpiling.

When a new antihypertensive drug is prescribed during the observation period subsequent to the index date – in addition to or in substitution of the first drug prescribed – a shorter denominator will be used (starting from the date of the first prescription for that new drug):

$$MPR = \frac{\text{number of days supply obtained during observation period}}{\text{number of days between first dispensing date and the end of observation period}} \text{ x } 100$$

Substitution or switching refers to discontinuation of one antihypertensive drug with initiation of a new drug within the duration of last prescription refill. When that happens, the denominator of the first drug prescribed (and that is discontinued) is the number of days between first dispensing date and the end of the theoretical end of the last dispensing.

For patients receiving multiple antihypertensive drugs, the MPR will be calculated for each drug separately, and the overall MPR will be the mean of the individual MPR values. As in other studies[33-38], a threshold of 80% will be used to dichotomize between good quality implementation and poor quality implementation or in common and simplified language, adherents and non-adherents.

Calculations of MPR greater than 100% will be set to 100% because even though a MPR > 100% may reflect patients refilling prescriptions before the end of their medication supply or hoarding medication for later use, it is unlikely that patients will actually use hypertension drugs at greater than the prescribed frequency.

Logistic regression will be used to estimate relative risk with 95% Confidence Intervals (CI) for poor quality implementation of the prescribed antihypertensive treatment. Adjustment of the model will be assessed by Hosmer-Lemeshow test.

Persistence, like initiation, is also a time-to-event variable with a well-defined time origin (initiation) and an end-point which is the time of treatment discontinuation. The end-point will be censored if it's not observed during the observation period, e.g. if the patient is a continuous user. It will be quantified as the proportion of patients not exceeding the maximum allowed treatment gap that a patient is allowed to have (which is 1 times the duration of the prescription after which the treatment gap occurs or 90 days, whichever lower) during follow-up. Kaplan-Meier analysis will be used to calculate persistence and 95% CI after one and two years. Cox proportional hazard regression will be used to estimate hazard ratios of potential predictors for discontinuation and 95% CI.

Therefore, a patient is considered a *continuous user* if the gap between any of his/her prescriptions in the 2-year period is < 1 times the theoretical duration of his/her last prescription or 90 days, whichever lower. A patient is considered a *discontinuous user* or *non-*

persistent if he/she had a consecutive 90-day period after the theoretical end date of a given prescription which they received no prescriptions for any antihypertensive medication. For those cases, the theoretical end date of the last prescription is defined as the discontinuation date. For patients using more than one antihypertensive drug, the last theoretical end date is defined as the discontinuation date, regardless of whether a simultaneously used drug was discontinued earlier, to increase specificity.

7.7. LIMITATIONS OF THE RESEARCH METHODS

Use of secondary databases, such as claims databases has a number of limitations, including the inability to determine if the patient actually consumed the dispensed medication. In this study, prescription refill records are being used as a proxy for actual medication taking process even though a prescription refill is not equivalent to ingestion of medication. However, it can be reasonable assumed that patients would not continue to refill a prescription without the intention to adhere. On the other hand, a patient may be classified as a discontinuous user because he was advised to do so by the physician for different reasons – even though that's not typical in hypertension treatment - or even the patient may have obtained his medication from sources not captured in the available data, such as sharing medication with others (e.g. family members), and obtaining medication directly from a pharmacy, without a prescription. In both situations, claims data lack on that information and poor implementation and/or discontinuation may be overestimate.

Another limitation of using secondary databases like SIARS is that it lacks on the indication for which the drugs are prescribed. With antihypertensive drugs, there is more uncertainty on the indication because they can also be prescribed for angina pectoris, heart failure, cardiac arrhythmias and other cardiovascular diseases. In studies like this, a relevant number of patients, who do not use antihypertensive drugs for hypertension and not for a chronic disease, can be incorrectly classified as discontinues users and/or patients with poor quality of implementation. To control for that, the cohort includes only patients with prescription of antihypertensive drugs and diagnosis of hypertension, expressed in K86 and K97 codes of ICPC-2.

A third limitation is concerned to the lack of information on dosage regimen in the database. Relaying on days' supply information for estimation MPR imply that information on that should be as accurate as possible. SIARS do not provide information on days supplied for prescriptions but do include amount dispensed. Therefore the number of days supplied will be estimated from standard medications references.

Finally, prescription data account only for primary care units. During the follow up period patients may receive prescriptions from other providers, including specialist and hospital outpatient settings and that information is not disaggregated at a patient level in SIARS.

Nevertheless, all filled-up prescriptions are captured at the claims database. Matching for patient's NHS number in every prescription will allow us to take those prescriptions into account for implementation and discontinuation measures.

In spite of these limitations, the use of rates of prescription refills is an objective method to calculate both adherence and persistence with chronic therapy. MPR is also the accepted standard for the evaluation of adherence using retrospective data; it's easy to calculate, and is the most commonly used metric, allowing for comparisons among studies. MPR is the best available measure for assessing adherence to hypertension medications using retrospective data.

8. Protection of human subjects

This is a fully register-based study and patients will not be contacted in any phase of the study. This study does not affect the treatment of the patients.

Patient data handled by the researchers are de-identified and therefore will not allow patient identification.

9. Management and reporting of adverse events/adverse reactions

This study does not meet the criteria for adverse events/adverse reactions reporting.

10. Plans for disseminating and communicating study results

This study is developed as a doctorate thesis. There will be also prepared scientific manuscripts for publication, during and after the study timeline.

An independent review of study results will be carried out by the thesis jury.

An abstract of the study will be provided through the ENCePP e-register of studies within three months following the final report. The abstract of the main results will be published, whether positive or negative.

11. Amendments and deviations

The review from the ethics committee of ARSLVT didn't change the protocol.

12. Competing interests

The authors declare they have no competing interests and no financial or non-financial conflicts of interest.

13. AUTHORS' CONTRIBUTIONS

All authors contributed to drafting the manuscript, refinement of the study protocol and approval of the final manuscript.

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15. FUNDING

This project has no funding.

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