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

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Tese para obtenção do grau de Doutor em Ciências da Vida
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SUMMARY

RATIONALE AND BACKGROUND: Cardiovascular disease is a major cause of morbidity worldwide, being responsible for up to 32% of all deaths in Portugal. Hypertension is highly prevalent and one of the major risk factors for cardiovascular disease. Over 42% of the Portuguese adults (18-90 years) would have hypertension. Even though the benefits of antihypertensive drugs in reducing the risk of major cardiovascular events have been extensively demonstrated, the control of hypertension continues to be inadequate. 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, but also fail to use it for a long uninterrupted period of time. A substantially poorer medication adherence rate is observed when analysing newly diagnosed patients, and accounting for those who fail to initiate treatment, fail to ever refill, and time after discontinue, rather than the more commonplace approach of only observing ongoing users. Conventional adherence measures therefore systematically underestimate the public health burden of poor medication adherence of newly prescribed medications.

OBJECTIVE: The main objective of this thesis is to determine adherence to antihypertensive therapy in newly treated hypertensive patients in primary health care units from Lisbon and Tagus Valley Region.

METHODS: This thesis reports data from a large, population-based, retrospective, cohort study that assessed adherence to antihypertensive therapy, in all its components, i.e., initiation, implementation and discontinuation, in newly diagnosed and treated hypertensive patients in primary health care units of Lisbon and Tagus Valley from January 1st to March 31st 2011 who used no antihypertensive drugs prior to January 1st 2011. We've also determined primary adherence rate to antihypertensive drugs, expressed as the number of claims records divided by the total number of prescriptions records. Data were collected from SIARS for each patient during a two-year period after the date of the first acquisition. Initiation was determined by the acquisition of a first prescription in a pharmacy within a six-month period. Implementation was quantified by estimation of Medication Possession Ratio and persistence was determined by the

proportion of patients remaining on any antihypertensive drug regardless of switching or the use of multiple drugs during follow-up. Persistence was analysed considering a maximum allowed treatment gap of 90 days. Reinitiation was also analysed. Initiation and persistence were analysed by Kaplan-Meier survival analysis and Cox proportional hazard regression was used to estimate hazard ratios for initiation and discontinuation. Logistic regression was used to estimate the odds ratio for poor implementation of the prescribed AHT therapy.

RESULTS: Overall primary adherence rate was 58.5%, increasing with age. Primary adherence rates were higher for men, patients living in the Lisbon Metropolitan Area and diagnosed with ICPC-2 code k87. Drugs acting on the Renin-angiotensin system had the highest primary adherence rates, increasing for fixed-dose combinations and diminishing with the increase of out-of-pocket cost for patients. Of the 10,204 cohort members, 493 (4.8%) never acquired any antihypertensive drug and 855 more (8.4%) initiated hypertension treatment with a considerable delay (six-months or longer) after the first prescription, being classified as 'non-users'. After adjustment for all the potential predictors of initiation, women, and patients aged 45-64 years, who received an initial prescription of with two or more drugs had higher initiation rates. Among patients with a first dispensing (n=8,856), 638 (7.2%) patients discontinued antihypertensive therapy after acquiring just the first prescription and 519 more (5.9%) completely discontinued treatment during the first year, making a total of 1,157 (13.1%) patients who were no longer on treatment at the end of the first year. During the second year, 904 (10.2%) more discontinued antihypertensive therapy. However, in spite of 6,157 patients being still on treatment two years after the initiation of hypertension treatment, only 539 (8.8%) of them were classified as continuous users, i.e. had no treatment gap or grace period of 90 days or longer, meaning that the remaining 5,618 (91.2%) were using antihypertensive therapy in an 'on and off' basis, discontinuing and reinitiating it over time. The risk of complete discontinuation was higher for younger patients, treated with monotherapy and followed by a single physician. Analysing the implementation of hypertension treatment in the two-year observation period, among patients with a first dispensing only 456 (5.1%) had in their possession antihypertensive drugs for 80% or more days, regardless the occurrence of lapses in implementation, i.e. treatment gap or grace periods of 90 days or longer, which occurred in 233 (51.1%) of this patients with a high level of implementation. Younger patients and with a higher

buying power had a higher risk for poor implementation. However, and in spite of increasing persistence, the use of more drugs during the follow-up decreased the medication possession ratio for this patients.

CONCLUSION: The results of this thesis confirm previous observations that in clinical practice hypertension treatment is frequently abandoned and poorly implemented over time. Our results demonstrated that almost one out of five (19.5%) patients either never initiated treatment, did it with a considerable delay (after six months or more after their first prescription) or completely discontinued it just after acquiring their first antihypertensive drug, being the risk for discontinuation most pronounced during the first year. Low adherence rates to antihypertensive therapy, in all its components, are an especially alarming finding, since this condition contributes greatly to the burden of mortality and morbidity from cardiovascular disease in Portugal. Until this thesis, little was known in Portugal about adherence to antihypertensive therapy, especially at a population level. With this thesis we demonstrated not just the patterns of adherence to antihypertensive therapy but also some possible risk factors for non-adherence.

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

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PUBLICATIONS

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Coelho A, Rodrigues C, Vilares C, Silva M, Costa M, Caetano PA, et al. Investigação sobre adesão à terapêutica na população portuguesa – uma revisão de âmbito. Revista Portuguesa de Medicina Geral e Familiar. Forthcoming 2016.

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ABBREVIATIONS AND ACRONYMS

ABC Project – Ascertaining Barriers for Compliance Project

ACEIs - Angiotensin converting enzyme inhibitors

AHT – Antihypertensive

ARBs - Angiotensin receptor blockers

ARSLVT – Administração Regional de Saúde de Lisboa e Vale do Tejo (Regional Health Administration of Lisbon and Tagus Valley)

ATC code - Anatomical Therapeutic Chemical code

BID – twice a day (from the Latin, *bis in die*)

BBs – Beta-blockers

BP – Blood pressure

CCBs - Calcium channel blockers

CI - Confidence Intervals

CV – Cardiovascular

CVD - Cardiovascular disease

DDD – Defined daily dose

DGS – Direção-Geral da Saúde (Portuguese Directorate-General of Health)

ESH/ESC – European Society of Hypertension / European Society of Cardiology

GP – General practitioner

HR – Hazard ratio

ICPC - International Classification of Primary Care

LMA – Lisbon Metropolitan Area

MPR – Medication possession ratio

NHS – National Health Service (SNS in Portuguese)

NUTS - Nomenclatura das Unidades Territoriais para Fins Estatísticos

OR – Odds ratio

PDD – Prescribed daily dose

PDC – Proportion of days covered

PHC – Primary Health Care

PHYSA Study - Portuguese Hypertension and Salt Study

QD – one a day (from the Latin, *quaque die*)

RAS - Renin-angiotensin system

RCT - Randomized clinical trials

RR – Relative risk

RRP - Recommended retail price

SIARS – Sistema de Informação da Administração Regional de Saúde (Information System of the Regional Health Administration)

SmPC – Summary of Product Characteristics

VALSIM - Epidemiological Study of the Prevalence of the Metabolic Syndrome in the Portuguese Population

WHO – World Health Organization

INTRODUCTION

SCOPE OF THIS THESIS

Hypertension is an important risk factor for the development of cardiovascular (CV) morbidity and mortality[1-7]; about half of all cardiovascular disease (CVD) combining mortality and morbidity, can be attributable to high blood pressure (BP)[1-3].

Fortunately, hypertension is also widely considered as one of the most preventable causes of CVD because of the availability of effective antihypertensive (AHT) drugs, whose benefits in reducing BP have been extensively demonstrated over the last decades[5-14].

All classes of AHT drugs which are now considered to be first line treatment for hypertension have shown a comparable reduction in CV complications[6-7,14]. Lowering systolic BP by 10 mmHg or diastolic BP by 5 mmHg reduces CV events (fatal and non-fatal) by approximately 25% and cerebrovascular events by 30%[14]. Compared to no treatment, AHT drugs have also demonstrated the potential to reduce the risk of CV mortality by 19% and the risk of all CV mortality by 10%[15].

However, the literature indicates that up to two thirds of patients with hypertension are not successfully treated[4,6,12]. In Portugal, the PHYSA (Portuguese Hypertension and Salt) Study shown that 23.4% of the Portuguese with hypertension are unaware of their condition, and overall, among hypertensive patients, only 42.5% reach a controlled BP below 140/90 mmHg[16].

It is therefore paradoxical that despite the availability of effective AHT drugs and the progress that has been made in the treatment of hypertension, the number of people whose BP is controlled is disappointingly low[12,17].

MANAGEMENT OF HYPERTENSION

The management of hypertension is based on two major approaches: a modification of lifestyle and the lifelong prescription of AHT drugs[4-7], being the latter the cornerstone of the medical management of hypertension[5-7,18]. Thus, the use of AHT drugs for long uninterrupted periods of time is important because incorrect use will lead to a less

effective treatment in daily practice than observed in randomized clinical trials (RCT)[18-22].

Therefore, patients who start hypertension treatment should be prepared to take AHT drugs for a lifelong period. Yet, patients often do not only fail to take their drugs as has been prescribed by their physicians, which is commonly designated by non-adherence, but also fail to use them for a long uninterrupted period of time, e.g. non-persistence[8,13,18,23-24], which will ultimately lead to a less effective treatment.

ADHERENCE AND PERSISTENCE

Although adherence and persistence are conceptually linked together, and even interchanged in medical literature, they refer to a different problem. Adherence to medications is defined as the process by which patients take their medications as prescribed, including three components: initiation, implementation and discontinuation[25]. It is usually expressed as a percentage or fraction of doses taken as scheduled[23,26]. In this context, non-adherence refers to problems such as missing doses - intentionally or not -, or short periods of so called 'drug holidays', periods during which patients consciously do not take their medications, but restart thereafter. This means that in case of non-adherence, a patient does have the intention to use treatment for longer periods, but not always as prescribed. The long-term consequence is that the full benefit of treatment cannot be obtained making the patient sub-optimally protected[18,25,27].

The term persistence is used to characterize patients that continue their treatment for a specified period of time. In case of non-persistence, patients completely discontinue the use of a certain drug or treatment regimen, in contrast to non-adherence where only some doses are omitted. Therefore, non-persistence constitutes an even greater barrier to attain treatment goals[25,28].

In this context, non-adherence and/or non-persistence to AHT therapy represent an important component of preventable CV morbidity and mortality[8-9,11-13], since their consequences seem to be the same as those for hypertension itself[27].

Non-adherence to and non-persistence with prescribed medications is a widely prevalent problem; analysis of the electronically monitored dosing histories of approximately 17,000 RCT participants revealed that, during a year of observed treatment, almost 40% of participants had discontinued taking the prescribed drug (including 4% who never initiated their treatment), and in addition, 15% of participants were occasionally omitting some of their prescribed doses[29].

USE OF PRESCRIPTION AND DISPENSING/CLAIMS DATABASES FOR QUANTIFICATION OF ADHERENCE TO MEDICATIONS

An appropriate quantification of adherence to medications is fundamental in everyday clinical practice. There are many different methods for assessing adherence to medications, which Osterberg and Blaschke[23] categorized as either direct or indirect.

With the development of several prescription databases in the 1980s, it became possible to observe large numbers of patients in real world clinical settings. This also provided researchers an easy and inexpensive opportunity to obtain information on patterns of use of multiple drug classes, including AHT drugs[30-33].

Rates of pharmacy refills, extracted from pharmacy dispensing/claims databases, can be used as a surrogate for adherence to medications – indirect method[23]. First, they reflect patients' decision to continue with treatment and secondly, patients' effort to obtain the prescribed medication as the first step towards taking it[34]. Rates of pharmacy refills by assessing whether patients fill (acquire) their prescribed medications over specified time intervals, allow the evaluation of the medication-acquisition behaviours[30,34].

Little is known in Portugal about adherence and persistence to AHT therapy, especially at a population level. To our best knowledge this is the first study in the country to quantify adherence with AHT therapy in its three components and including all AHT drug classes at a population level, using prescription and dispensing/ claims databases. Previous studies[35-41] were focused on local populations and quantified adherence to AHT therapy using questionnaires and/or interviews of patients. With the exception of Costa et al study[41], all studies evaluated only the component of implementation of AHT therapy. A recent study[42] conducted in the Alentejo Health Region also evaluated AHT

therapy using prescription and dispensing/claims databases, though it was focused on just one AHT drug class.

OUTLINE OF THIS THESIS

The main objective of this thesis is to determine adherence to AHT therapy in newly treated hypertensive patients in Primary Health Care (PHC) units from Lisbon and Tagus Valley Health Region, in its three components – initiation, implementation and discontinuation. Additionally, we aim to identify risk factors for non-adherence and non-persistence.

This thesis is divided into seven chapters. In chapter one to three, we present the theoretical framework on adherence to medications, focusing on hypertension. Chapter one specifically focuses on hypertension prevalence, definition and classification, and also treatment recommendations. In this chapter, we also describe the relationship between BP control and adherence to medications, building a bridge for chapter two, where we provide a conceptual framework on adherence, in its various definitions and issues. We also describe risk factors for non-adherence, using the five categories defined by the World Health Organization (WHO) as a reference.

In chapter three, we describe different methods for quantification of adherence to medications, focusing on rates of pharmacy refill.

In chapter four we describe the objectives of this thesis and in chapter five we describe in detail, the methodological issues of the study design, including a previous description of the local context where the study was conducted. Special attention was dedicated to exposure definitions and measures used in this thesis for determining the several rates of adherence.

In chapter six we present the main findings of our study, accordingly to the different components of adherence – initiation, implementation and discontinuation.

Finally, in the discussion chapter – chapter seven – the results of this thesis are compared to the published literature on adherence to AHT therapy and put in

perspective and the novelty of our findings, but also the study limitations are emphasised.

To comply with NOVA Medical School recommendations, at the end of this thesis we've included a summary (in a more extension version) in Portuguese.

CHAPTER 1: HYPERTENSION

1.1. PREVALENCE OF CARDIOVASCULAR DISEASE: FOCUS ON HYPERTENSION

CVD is the main cause of premature death in industrialised countries[1-3,43] and is also a major cause of morbidity worldwide, as well in Portugal[16,44] where it is responsible for up to 32% of all deaths[10].

The high prevalence of hypertension worldwide has played a major contribution to the global burden of disease associated to CVD. Almost ten years ago, Kearney and colleagues[1] analysis indicated that more than a quarter of the world's adult population had hypertension in 2000, and that this proportion would increase to 29% by 2025 – less than ten years from now. Overall, the prevalence of hypertension appears to be around 30-45% of the European population, increasing with age[6].

For the last 30 years, Portugal has been among the countries with the highest levels of mean BP[45]. It has been estimated that overall, over 42% of the Portuguese adult population aged 18 to 90 years, would have hypertension[16,44]. In 2008, the prevalence of hypertension (or the use of AHT drugs as a proxy for hypertension) in adults aged ≥25 years was estimated at 41.9%[45].

1.2. HYPERTENSION AND CARDIOVASCULAR RISK

Hypertension has been identified as the leading risk factor for mortality[1-3], and is ranked third as a cause of disability-adjusted life-years[3]. Its importance derives not only because of its high frequency – it is in fact, the most common chronic disease in developed countries - but also because it is a major modifiable/reversible risk factor for CV and kidney disease[1,4-6,12-13].

A CV risk factor corresponds to a biological or behavioural characteristic of an individual, which is, independently related to the subsequent development of CVD and/or CV event, increasing the probability of their occurrence. Any major risk factor, such as hypertension, if left untreated for many years, has the potential to produce CVD. Risk factors are typically, surrogates for deeper causes (and better predictors) of CVD[46-48].

Hypertension was perhaps the first well-established CV risk factor. Regardless of the underlying cause of high BP, hypertension directly contributes to CVD risk and it predicts CVD[46]. From tensional values of 115/75 mmHg, CV risk doubles for each 20 mmHg increase in systolic BP and 10 mmHg increase in diastolic BP[49].

In addition, hypertension contributes to the prevalence of other CV risk factors, such as insulin resistance, lipid abnormalities, changes in renal function, endocrine abnormalities, obesity, left ventricular hypertrophy, diastolic dysfunction, and abnormalities in vascular structure and elasticity[50]. When concomitantly present, high BP and other CV risk factors may potentiate each other, leading to a total CV risk[i] that is greater than the sum of its individual components[6].

Thus, since only a small fraction of the hypertensive population has an elevation of BP alone, with the majority exhibiting additional CV risk factors, the 2007 and the more recent 2013 European Society of Hypertension / European Society of Cardiology (ESH/ESC) guidelines for the management of arterial hypertension[6], as well the Portuguese Directorate-General of Health Clinical (DGS) Standard[10] emphasize that management of hypertension should be related to quantification of total CV risk.

1.3. DEFINITION AND CLASSIFICATION OF HYPERTENSION

As mentioned, the association between lack of BP control and CV risk and premature death has been extensively demonstrated[1,6,10,43,51]. It is a continuous, consistent and independent of other risk factors relationship – the higher the BP, the greater the chance of stroke, ischemic heart failure, congestive heart disease failure, and renal failure[4-6] and the shortening of life expectancy up to 5 years[52].

[i] Total CVD risk is defined as the probability of an individual's experiencing a CVD event (e.g. heart failure, myocardial infarction or stroke) over a given period of time, for example 10 years. Total CVD risk depends on the individual's particular risk factor profile, sex and age; it will be higher for older men with several risk factors than for younger women with few risk factors. The total risk of developing CVD is determined by the combined effect of CV risk factors - an individual with several mildly raised risk factors may be at a higher total risk than someone with just one elevated risk factor[48].

The continuous relationship between BP and CV and renal events makes the distinction between normotension and hypertension difficult when based on cut-off BP values[6]. In practice, however, cut-off BP values are universally used, both to simplify the diagnostic approach and to facilitate the decision about treatment[6].

Hypertension is defined as values ≥140 mmHg systolic BP and/or ≥90 mmHg diastolic BP, based on the evidence from RCT that in patients with these BP values treatment-induced BP reductions are beneficial[5-6,10]. BP levels definition and classification accordingly are shown in Table 1.

Table 1: Definitions and classification of office blood pressure levels

Category	Systolic		Diastolic
Optimal	<120	and	<80
Normal	120-129	and/or	80-84
High normal	130-139	and/or	85-89
Grade 1 hypertension	140-159	and/or	90-99
Grade 2 hypertension	160-179	and/or	100-109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

Table adapted from Mancia, et al[6]

1.4. HYPERTENSION TREATMENT

Not only the association between lack of BP control and CV risk has been extensively demonstrated; the benefits of AHT therapy in reducing the risk of major CV events have also been[5-14]. Lowering BP is associated with significant decreases in the incidence of stroke, ischemic heart failure, congestive heart disease failure, and renal failure, irrespective of age, gender, type of AHT used, or severity of hypertension[5-7,13-15,49].

Numerous large-scale clinical trials, such as the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[53] and the Hypertension Optimal Treatment (HOT) trial[54], have demonstrated the benefits of BP control to reduce CV mortality and morbidity in patients with hypertension.

Hypertension treatment is based on two major approaches: lifestyle changes and the lifelong prescription of AHT drugs[4-7]. In the short term, it aims to reduce and control BP to below 140/90 mmHg if AHT drugs are tolerated and not contraindicated. In the long-term, the goal of AHT therapy involves countering the progression of the disease and its impact on target organs and therefore reducing CV morbidity and mortality as a result of hypertension[48].

Appropriate lifestyle changes are fundamental for the prevention of hypertension[6]. It has been also widely demonstrated that CVD is strongly associated to lifestyle, especially the use of tobacco, unhealthy diet habits, physical inactivity, and psychosocial stress[55].

The World Health Organization (WHO) has stated that over ¾ of all CVD mortality may be prevented with adequate changes in lifestyle[55]. Lifestyle changes are also important for hypertension treatment: BP-lowering effects of targeted lifestyle changes can be equivalent to drug monotherapy. However, such changes should never delay the initiation of drug therapy in patients at a high level of risk[6-7].

The recommended lifestyle changes that have been shown to be capable of reducing BP are: (1) salt restriction, (2) moderation of alcohol consumption, (3) high consumption of vegetables and fruits and low-fat and other types of diet, (4) weight reduction and maintenance and (5) regular physical exercise. In addition, insistence on cessation of smoking is mandatory in order to improve CV risk, and because cigarette smoking has an acute pressor effect that may raise daytime ambulatory BP[6].

Although counselling about lifestyle changes plays a role, lifelong prescription of AHT drugs remains the cornerstone of the medical management of hypertension[5-7,18]. CV drugs (such as statins, AHT, and antithrombotic agents) remain the most common medical interventions worldwide for both primary and secondary prevention of CVD, through modification of intermediate determinants of CVD[56], such as hypertension.

The 2013 ESH/ESC Guidelines[6] state that diuretics (including thiazides, chlorthalidone and indapamide), beta-blockers (BBs), calcium channel blockers (CCBs), angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are all

suitable for the initiation and implementation of hypertension treatment, either as monotherapy or in some combinations.

In Portugal, a study performed in the Primary Health Care (PHC) setting, the VALSIM (Epidemiological Study of the Prevalence of the Metabolic Syndrome in the Portuguese Population) Study, involving 719 general practitioners (GP) and representative of all regions of the Country identified diuretics (47.4%), ARBs (43%) and ACEIs (39.2%) as the most frequently used AHT drugs for hypertension treatment of the population[57].

The previous ESH/ESC Guidelines, back in 2007, underlined that, no matter which drug is employed, monotherapy can effectively reduce BP in only a limited number of hypertensive patients and that most patients require the combination of at least two drugs to achieve BP control[5]. The VALSIM Study also found that the proportion of hypertensive patients under monotherapy was still very high, implicating that increasing the use of combination AHT therapy would probably improve BP control in the population[57]. Also the PHYSA study found that among patients with hypertension controlled, 39.2% were on monotherapy and 56.4% were on combination therapy[57], which corroborates that the use of combination AHT therapy improves BP control.

Thus, the issue is not whether combination therapy is useful, but whether it should always be preceded by an attempt to use monotherapy, or whether - and when - combination therapy may be the initial approach[6]. The 2013 ESH/ESC Guidelines[6] and the DGS clinical standard[10], therefore favors the use of combinations of two AHT drugs at fixed doses in a single tablet.

Additionally, DGS recommends the following principles in AHT therapy: (1) use of generic drugs whenever appropriate and cost-effective; (2) use, where possible, of QD (one a day) dosing regimen; (3) if the patient is properly controlled with different therapeutic option, it should be maintained and justified in the clinical record[10].

1.5. ADHERENCE TO MEDICATIONS AS A BARRIER TO BLOOD PRESSURE CONTROL

Despite the excellent array of effective, well-tolerated drugs used in hypertension treatment, its control continues to be inadequate[6,12-13,17]. Reports suggest that up to two thirds of patients with hypertension are not successfully treated, that is, achieve BP control[4,6,12]. In Portugal, the PHYSA study[16] found that among hypertensive patients, 76.6% are aware of their high BP and 74.9% are treated; among treated patients, 55.7% have their BP controlled and in the overall hypertensive population the rate of control is 42.5%, which represents a 3.8 times higher control than it was found in an earlier study also in the Portuguese population[44]. Still, these figures show that there is a large place for improvement and hypertension remains a silent and undertreated CV risk factor[49].

The precise reasons for patients not achieving target BP despite being treated are not completely clear yet. Still, three main causes of the low rate of BP control have been identified: (1) physician inertia[ii] (2) patient low adherence to treatment, and (3) deficiencies of healthcare systems in their approach to chronic diseases[6]. In this context, low adherence to treatment is perhaps the most important cause of the low rate of BP control[8,13,23-24].

A recent systematic review and meta-analysis of epidemiological studies estimated that 9% of all CV events in Europe could be attributed to non-adherence to CV drugs alone[56]. In the *Heart and Soul* study[58] which examined the impact of self-reported adherence, the authors found CV events to be almost twice as high in non-adherent participants and remained independently predictive of adverse CV events after adjusting for baseline disease severity and other known risk factors. Additionally, discontinuation, e.g. non-persistence with AHT therapy in primary prevention increases the risk of acute myocardial infarction and stroke[59].

[ii] Lack of therapeutic action when the patient's BP is uncontrolled. It's generated by several factors, such as: doubts about the risk represented by high BP, particularly in the elderly, fear of a reduction in vital organ perfusion when BP is reduced and concern about side effects. Several physicians also maintain a skeptical attitude towards guidelines because of their multiplicity and origin from different sources, which make their recommendations sometimes inconsistent[6].

Many different studies have demonstrated the relationship between adherence to AHT therapy and BP control and CV risk, as follows:

i. A meta-analysis by DiMatteo et al[61] reported that patients who adhered to AHT therapy were 3.44 times more likely to achieve good BP control than those who were non-adherent;
ii. Bramley et al[24] reported that highly adherence patients were 45% more likely to achieve BP control than patients with medium or low levels of adherence;
iii. Corrao et al[62] found that high adherence to AHT therapy was associated with 22% decreased risk of CV events compared with lower adherence. The authors also found that persistent patients had a 37% reduction of coronary and cerebrovascular risk compared to discontinuers;
iv. Mazzaglia et al[63] found that high adherence to AHT therapy was associated with a 38% decreased risk of CV events compared with lower adherence;
v. Dragomir et al[64] found that low adherence was associated with an increased risk of coronary and cerebrovascular disease as well as chronic heart failure by 7%, 13% and 42%, respectively, and an increased rate of hospitalization of 17%. This increased risk for vascular events was also associated with substantial costs (35% more compared to the costs if patients have been high adherent);
vi. Pittman et al[65] also found that non-adherence to be associated with greater healthcare utilization as demonstrated by CV-related hospitalizations (OR=1.33) and emergency department visits (OR=1.45);

All this different studies demonstrate that in the longer term, the inadequate control of BP that culminates from non-adherence to CV drugs means that patients remain at significant risk for costly micro- and macro vascular complications that can result in premature mortality[18].

That's why hypertension guidelines[4-7,10] recognize that "…the most effective therapy prescribed by the most careful clinician will control hypertension only if the patient is motivated to take the prescribed medication and to establish and maintain a health-promoting lifestyle"[4]. This statement clearly emphasizes the importance of supporting adherence to and persistence with treatment for patients to gain the maximal benefits of their long-term therapy[66].

Therefore, treatment, control and prevention of the consequences of hypertension, depend on adherence to interventions as much as on those interventions' efficacy and tolerability[11,67-68]. Adherence to AHT therapy may be the link between disease management and attainment of the desired therapeutic result[29,69] since high-adherent patients have a lower risk of major CV events, hospital admissions and global health care costs[20,62-65,69].

Non-adherence and/or non-persistence are an important component of preventable CV morbidity and mortality[8-9,11-12], since the consequences of poor adherence and persistence with AHT therapy are the same as those for hypertension itself[27].

Although this association between medication non-adherence and adverse outcomes has been demonstrated in many observational studies, some concern has been raised that this association may be, at least in part, related to a 'healthy adherer' effect[70-71]. The healthy adherer effect implies that the lower risk of adverse outcomes associated with adherence may be a surrogate marker for overall healthy behaviour[56]. This is supported by post hoc analyses of RCT in which even adherence to placebo is associated with better outcomes than for patients who are non-adherent to active treatment, i.e. participants in RCT who do not follow medications regimens or placebo regimens have a poorer prognosis than subjects in the respective groups who do[23,60]. It appears that patients who take their medication regularly are also more likely to perform other healthy behaviours, such as eating properly and exercising regularly[56,71], which is not measured directly in prospective or retrospective studies.

However, there is also evidence against the healthy adherer effect being a major factor in observed associations between medication adherence and outcomes. Based on the differential class effects of adherence to medication on long-term survival, it has been suggested that adherence related benefits are mostly mediated by drug effects rather than by healthy adherer behaviours[64]. Although the debate will continue, the medications under study have often been demonstrated in RCT to be efficacious, and therefore, the importance of taking these medications as prescribed should be reinforced.

CHAPTER 2: ADHERENCE TO MEDICATIONS

2.1. ADHERENCE TO MEDICATIONS: PREVALENCE AND CONSEQUENCES

As expressed in the previous chapter, adherence to prescribed medications (or medication adherence) is crucial for therapeutic success, because even the most effective and rational pharmacological/medical interventions can be ineffective by suboptimal adherence (e.g. partial or complete non-adherence) to them[72]. Suboptimal or partial adherence has been highlighted as a significant obstacle in achieving better patient outcomes[23,73] by reducing the effectiveness of prescribed medications. That translates not just in to a missed opportunity for the treatment's effect, but also in increased healthcare costs[74], since the commonly recurring patterns of non-adherence create a catalog of therapeutic errors (e.g. failed treatment, inappropriate drug escalation, hazardous rebound or recurrent first-dose effects, and even misdiagnosis), all of them carrying economic costs[72].

Though for many chronic diseases, such as hypertension, pharmacological options are available and, in fact, effective as demonstrated in RCT, patients often do not only fail to take their medication as has been prescribed by their physician - non-adherence - but also fail to use it for a long uninterrupted period of time - non-persistence[23]. Population-based studies using pharmacy refill rates have demonstrated that patients typically obtain less medication than they have been prescribed[30,42,75].

Full recognition of partial/suboptimal adherence or non-adherence to prescribed medications is based on discrepancies between the patient's dosing history and the prescribed dosing regimen[29]. Thus, non-adherence as well as non-persistence constitutes major barriers to controlling chronic diseases leading to an increased morbidity and mortality[67,72], since as Osterberg and Blaschke[23] stated "(…) it is clear that the full benefit of the many effective medications that are available will be achieved only if patients follow prescribed treatment regimens reasonably closely".

As the burden of disease in the population continues to shift toward chronic diseases - it has been estimated that the global economic impact of chronic diseases will continue to grow by 2020, at which it will correspond to 65% of healthcare costs worldwide -, the problems created by patient's non-adherence to long-term therapies gain in importance[50,67,72].

Due to its high prevalence, the costs specifically related to hypertension, are substantial. The financial impact of hypertension stems not only from the treatment of high BP, but also from the costs of managing the chronic diseases linked with this medical condition[64].

Adherence to medications plays in this context, a key role in the clinical management process[76]. The issue has a global relevance particularly in wealthier nations, where access and use of healthcare systems are high, and further increasing the effectiveness of a medication could rely largely on improving adherence levels[77].

As mentioned in the Introduction of this thesis, non-adherence to prescribed medications is a widely prevalent problem; it has been estimated that during the first year of observed treatment, almost 40% of participants discontinue taking the prescribed drug (including 4% who never initiated their treatment), and in addition, 15% of participants occasionally omit some of their prescribed doses[29]. A WHO previous report[11] on adherence to long-term therapies has estimated that one in every two patients in developed nations do not adequately adhere to long-term therapies. More recently, a systematic review and meta-analysis of epidemiological studies conducted by Chowdhury et al[56] demonstrated that the proportion of patients with good adherence to CV drugs is approximately 57%.

Considering these figures, it has been suggested that increasing the effectiveness of methods for improving adherence may have a far greater positive impact on human health and its economics than any single improvement in medical treatment[78]. For this reason, adherence to medications has been called the “next frontier in quality improvement” and is an important part of CV outcomes research[79] since poor adherence itself is a problem that should be viewed as “diagnosable and treatable”[80].

2.2. MEDICATION ADHERENCE DEFINITION

Over time, a variety of terms have been used to define different aspects of the act of seeking medical attention, acquiring prescribed medications and taking those prescribed medications appropriately. These terms include ‘compliance’, ‘concordance’, ‘adherence’ and ‘persistence’. Although often used interchangeably, these terms imply different views about the relationship between patients and healthcare professionals[25,29,72].

The term ‘compliance’ represents the traditional approach to prescribed medications and taking them. It was initially defined as “the extent to which a person’s behaviour coincides with the clinical perspective”[81]. Introduced in 1975 as an official Medical Subject Heading (MeSH) in the United States National Library of Medicine, it has a widely perceived, somewhat negative connotation that patients are subservient to prescribers[25]. In fact, during early research on this topic, the role of patient’s views on medication adherence was perfectly neglected. Within this medical dominance perspective, the patient should passively obey to the prescriber’s instructions; any deviation should be considered the patient’s only responsibility and therefore, the patient should be blamed for it[17,25,60,67,82].

The term ‘compliance’ has been increasingly replaced by ‘adherence’, as the latter has been thought to evoke more the idea of cooperation between prescriber and patient. To the WHO, medication adherence can be defined as “the extent to which a patient’s behaviour, with respect to taking medication, corresponds with agreed recommendations from a healthcare provider”[11].

The shift from ‘compliance’ to ‘adherence’ reflects a fundamental change in understanding relationships between patients and healthcare professionals[25,67].

It was in the light of this shift that the term ‘concordance’ was proposed, originally to describe the patient–prescriber relationship. The ‘concordance’ construct recognized the need for patients and healthcare providers to cooperate in the definition of a mutually agreed treatment programme, acknowledging that patients and providers may have

divergent views. However, this term is sometimes incorrectly used as a synonym for 'compliance'[25].

Another term, 'persistence', or continuation, is used to characterize patients that continue on treatment for a defined period of time. In case of non-persistence, patients completely discontinue the use of a certain drug or treatment regimen, in contrast to non-adherence where only some doses are omitted[25,83]. Although adherence and persistence are both components of appropriate medication use, they have differing clinical implications[84]. The effects of non-adherence may be less overt; observed changes in BP may be less dramatic than those seen with non-persistence[86], therefore, non-persistence constitutes an even greater barrier to attain treatment goals.

Figure 1 shows different patterns of execution/implementation and discontinuation of AHT therapy.

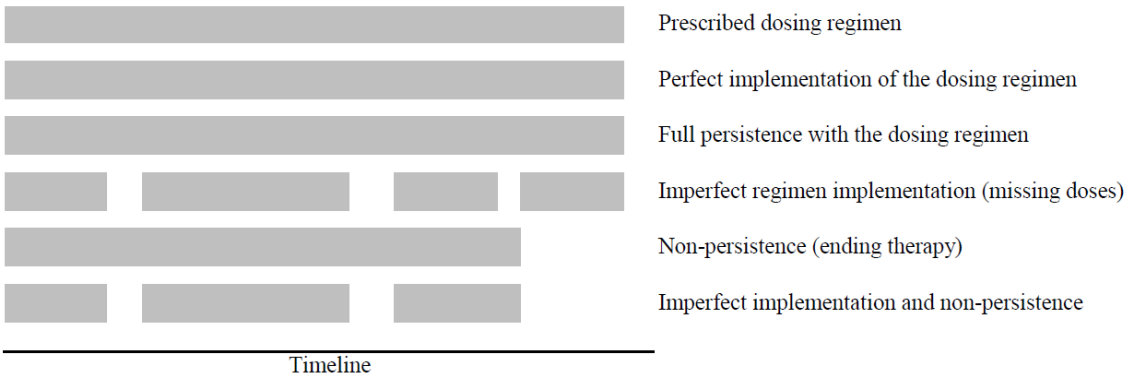

Figure 1. Differences between adherence and persistence (adapted from Lowy[87])

In light of all this, although many studies have examined adherence to medications over many years, the absence of a common taxonomy and the lack of reliable measurements of ambulatory patients' exposure to prescribed medications have resulted in much confusion, with adherence rates ranging from 15% to as high as 97%[62,68,87-88].

Also, a number of population-based studies have demonstrated high discontinuation rates varying from 35% to 84%[19,28,90-95]. Cramer et al[96] in their review demonstrated that is a statistically significant trend towards decreased persistence with time. Other studies show that non-persistence continues to reduce the number of patients still engaged with AHT drug dosing regimens out to five years or more after the onset of treatment, by

which time only 10% to 15% of the originally treated patients are still engaged with the regimen[97].

Thus, the wide range of adherence and persistence (or discontinuation) rates in published studies is presumably a reflection not only of the range of methodologies and AHT drugs that have been used but also of the number and complexity of reasons for poor medication-taking behaviour[18].

In 2012, a European consensus on terminology was proposed by the European Union-sponsored 'Ascertaining Barriers for Compliance' Project (ABC Project)[77], in which adherence to medications is defined as "the process by which patients take their medications as prescribed"; medication adherence consists of three elements: 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. Adherence is essentially a dynamic process, with sometimes slow-to-change effects on drug actions of variable exposure to prescribed drugs"[25]. Recognition of the dynamic nature of medication adherence is important when considering ways in which poor medication-taking behaviour could be improved[18].

The process starts with initiation of the treatment, which occurs when the patient takes the first dose of a prescribed medication, after its acquisition from a pharmacy[25,30]. The intervening part of the process is implementation of the dosing regimen, defined as "the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose is taken". The process ends (discontinuation) when the patient stops taking the prescribed medication[25]. Persistence represents the accumulation or length of time from initiation to discontinuation of therapy[18,25].

So, non-adherence to medications can occur in the following situations or combinations thereof: late or non-initiation of the prescribed treatment, sub-optimal implementation of the dosing regimen and/or early discontinuation of treatment[25].

Non-adherence can also be looked at as being intentional or non-intentional. Intentional non-adherence is an active process whereby the patient chooses to deviate from the

healthcare provider's recommendations. This may be a rational decision process in which the individual weighs the risks and benefits of treatment against any adverse effects; the patient consciously self-adjust its regimen, or prematurely terminate medication use, because of side-effects and toxicity, personal beliefs or convenience. Unintentional non-adherence is a passive process in which the patient may unintentionally fail to fill the prescription, forget a dose or may take it incorrectly because misunderstanding or forgetfulness of healthcare provider's instructions[11,84,98-100].

As a consequence, intentional versus non-intentional non-adherence patients may struggle with different adherence determinants, requiring different interventions[11].

2.2.1. First element of the adherence process: initiation

Initiation is often reported as the time from the first prescription until first dose is taken. It is thus a time-to-event variable with a well-defined time origin (prescription) and an end-point which is the first dose taken, usually designated as index date[25].

In the literature, the terms 'primary adherence'[101-102], 'first-fill adherence'[103] and 'initial medication adherence'[104] are also used. Primary adherence or initial medication adherence refers to a new prescribed medication being dispensed at a pharmacy (acquired or sold) within a defined number of days after it was prescribed[101-105]. It is a discrete event that assesses whether or not the patient received the first prescription[101-105].

By opposition, primary non-adherence can be defined as a failure to have a new prescription dispensed (patient did not acquire the first prescription) within a defined number of days after the medication was prescribes[101,106-107].

Though it's a recent concept, a number of population-based studies have demonstrated high primary non-adherence rates varying from 4.7% to 33%[41,64,101,108-113].

In the literature, the term 'primary adherence' is often described as the acquisition of prescribed medications in opposition to 'secondary adherence', the actual medicine-

taking behaviour once the medications have been purchased[41]. In the conceptual model proposed by Raebel et al[101], 'secondary adherence' is an ongoing process that measures whether or not the patient received dispensings or refills as prescribed during a defined observation period.

Shrank et al[107] found that new users of medications had more 2.74 times greater probability of not acquiring their prescribed medications than prevalent users. The authors also found that maintenance (on going) medications had slightly higher probability of being acquired. Other studies found that a prescription of a new medication for a new medical condition has a lower probability of being filled in a pharmacy, comparing to a new medication prescribed for an ongoing condition[109,111-112].

Additionally, several studies on adherence to medications have demonstrated that many patients interrupt their treatment, shortly after the acquisition in a pharmacy of its first prescription[11]. This is called 'early discontinuation' or 'short persistence'[29,111].

The failure to distinguish between the quality of execution or implementation while the patient is engaged with his or her dosing regimen and early discontinuation has led to the widespread belief that overall adherence in hypertension treatment is only about 50-60%[114]. The distinction between these two aspects of the patients' adherence to a prescribed regimen is crucial because the dynamics as well as the clinical and economic consequences of poor quality of execution and short persistence can differ markedly[115].

Different studies[13,106,108] show that a substantially poorer medication adherence rate is observed when using a new prescription cohort, and accounting for those who fail to initiate the new medication (primary non-adherence), fail to ever refill (early discontinuation or short persistence), and time after discontinue treatment, rather than the more commonplace approach of only observing ongoing users.

However, many adherence studies systematically exclude patients with primary non-adherence or early non-persistence, since they rely on pharmacy dispensing or claims databases[11,105]. By definition, pharmacy claims databases do not contain information about medications prescribed but never dispensed (i.e., primary non-adherence). Furthermore, medications dispensed only once but never refilled (i.e., early non-

persistence) do not meet the minimum criterion of two dispensings required to calculate the commonly used metrics for medication adherence calculations[26,101-102,109]. As a result, conventional adherence measures therefore systematically underestimate the public health burden of poor medication adherence for newly prescribed medications[11].

2.2.2. Second element of the adherence process: implementation

Lapses in implementation occur in the context of ongoing treatment when patients modify their dosing regimen. They are typically a consequence of forgetfulness or negligence[41,99] (i.e. non-intentional or non-intentional non-adherence): most of such errors involve a single day's dose, but some represent 'drug holidays', which are an important aspect of patient non-adherence[11,23,25,115]. Drug holidays are a multi-day sequence of omitted doses, thus giving rise to exceptionally long intervals between sequential doses[25,100,116]. Still, the occurrence of longer lapses in dosing seems to be less frequently than shorter lapses[115].

Typically, there are six general patterns of implementation of dosing regimen: (1) close to perfect adherence; (2) taking nearly all doses with some timing irregularity; (3) missing an occasional single day's dose, and some timing inconsistencies; (4) taking drug holidays 3 to 4 times per year; (5) taking drug holidays monthly or more often and have frequent omissions; and (6) taking few or no doses[117-118].

In addition, it is common for patients to improve their medication-taking behaviour shortly before and after an appointment with a healthcare provider, which has been termed 'white-coat adherence'[119-120]. This phenomenon eloquently demonstrates the dynamics nature of medication-taking behaviour[18].

2.2.3. Third element of the adherence process: discontinuation

Discontinuation marks the point in time when the patient stops taking the prescribed medication[25]. It occurs when the next due dose is omitted and no more doses are taken thereafter[105]. The length of time from initiation to discontinuation is called persistence[18,25].

Persistence is the continued use of a medication or medications (i.e. no discontinuation) for a specified period of time, quantified from the index date (first dose taken) until the date of treatment discontinuation. Persistence is commonly determined as a dichotomous variable for a specified period of time; for example, was a patient persistent at 6 months or at 1 year? The proportion of patients persistent at a given time and the average duration of persistence (i.e. the average time from treatment initiation to discontinuation) can then be calculated[25,84]. It implies that the patient must have exhibited at least primary adherence because persistence over time cannot be measured unless the patient has received at least the first dispensing[101].

Persistence can be defined in terms of medication persistence, regimen persistence or therapy persistence[84].

Medication persistence is the time on a given medication, from its initiation to the end of the study period or the end of the last dispensed prescription for that medication before discontinuation of that medication[84].

Regimen persistence is the time on a specified set of medications from initiation with that set to any change in the set of medications being received (additions or discontinuations) or the end of the study period. This metric is used to evaluate persistence with combination therapy involving two separate medications, for example, an ACEI and a diuretic that are not a single, combined drug. This approach goes beyond medication persistence in that the period of regimen persistence ends if any part of the overall treatment regimen is changed[84].

Finally, therapy persistence is the time on any medications, from initiation of therapy to discontinuation of all medications or the end of the study period. This metric is similar to that for medication persistence but allows for the duration of persistence to continue for the entire period that a patient receives any medication. It's the most commonly used persistence definition used in the published literature[59,84,93-95,121]. In the case of hypertension treatment it is therapy persistence rather than medication persistence that matters[93], due to substantial evidence that the major drug classes do not differ in their ability to protect against CV risk caused by hypertension[4-7].

The use of any persistence definition implies that several types of changes in medication use should be accounted for, especially switching and additions.

Switching refers to discontinuation of one medication with initiation of a new one at approximately the same time. 'Approximately the same time' is subject to interpretation; this can be within a specified window around the discontinuation event, based either on a fixed period of time (e.g. one month) or on the duration of one medication refill[84].

In hypertension treatment, early switching (i.e. shortly after initiation of a therapy) is likely to reflect adverse events, whereas switching after a longer period may reflect failure of reaching BP control. However, AHT drugs may also be switched if a patient develops other medical conditions (e.g. diabetes or congestive heart failure) and requires a different drug either to treat both hypertension and the new condition or to avoid contraindications with the new condition or other newly initiated drugs. Therefore, switching may not always indicate a treatment failure[84].

Additions of new AHT drugs may also represent clinical failures (i.e. inability to control BP using the current treatment regimen), although medications can be added to treat newly diagnosed conditions. However, additions do not affect evaluations of treatment adherence, because they do not involve changes in the use of the medication or medications being assessed. Furthermore, additions may or may not be considered failure events with respect to the determination of persistence, depending on the analysis being performed. In assessing medication persistence or therapy persistence, additions do not affect persistence, whereas the addition of new AHT drugs is viewed as discontinuation of the previous regimen in evaluating regimen persistence[84].

Lack of persistence often occurs when patients discontinue therapy without instructions from or even discussions with their healthcare provider. Whereas patients who rapidly achieve target BP generally show increased persistence, patients who do not achieve BP control or those who show some reluctance against the prescribed drug, experience adverse effects (or perceived them to be associated with the prescribed drug) or even don't care with regard to provider's instructions may be tempted to modify their

medication doses or just discontinue them. This may occur early in a course of therapy and generally there is no immediate symptomatic consequences of doing so[84,86].

In the context of life-long therapy like AHT therapy, discontinuation may occur in response to the prescriber's decision to halt the treatment, but most often it is the result of a unilateral action by the patient, without the knowledge of the prescriber[99,122]. It has been estimated that during the first year of treatment up to 50% of patients discontinue their AHT therapy[13,115,123-124]. Most patients decide during the first year of treatment to continue or not and this decision is likely to last for a long time[28]. In an early study, among patients with newly diagnosed hypertension, for example, 78% were persistent at one year and only 46% at 4.5 years[92].

Because many patients may restart treatment at any point in time, Arnet et al[115] proposed the introduction of the quantification of *reinitiation* of treatment, as the proportion of patients with a dispensing after the predefined criteria for discontinuation (e.g. maximum 'allowed treatment gap' or 'grace period').

2.3. IMPLICATIONS OF NON-ADHERENCE AND NON-PERSISTENCE ON CLINICAL PRACTICE

On everyday clinical practice, if BP is not normalized with an initially prescribed regimen, prescribers may assume that the resulting lack of BP control is because of a lack of medication effectiveness rather than lack of medication use and respond by intensifying clinical measures with higher doses of medication - thereby increasing the risk of adverse effects, misdiagnoses, unnecessary treatment and further worsening of pre-existing illnesses – or substituting the initial drug or adding another AHT drug[29,56,83-84]. Therefore, non-adherence and non-persistence may therefore lead to unnecessary adjustments of drug regimens, being early discontinuation a predictor of occurrence of changes of AHT therapy[83].

The physician is faced with a question: Did the drug fail or did the patient fail to use it? If the dose is increased, adverse effects could increase. If the drug is changed, the risks and costs of switching are incurred[69]. Burnier et al[125] assessed patients presumed to

have drug-resistant hypertension. They found that nearly half of drug-resistant hypertensive patients were, indeed, non-adherents. The authors noted that "without any objective measurement of drug compliance, physicians have become used to opting almost always (...) for enhancing doses or prescribing new drug combinations (...) However, there is usually no rational basis for this decision".

So, starting with the assumption that patients with a variety of medical disorders take approximately half of medication as prescribed, prescribers should look for poor compliance, as a reason for ineffectiveness of a treatment[69]. However, there is little evidence that healthcare providers recognise patient adherence as an important factor in therapy; Heisler[126] concluded that patient's prior medication adherence has little impact on prescriber's decisions about intensifying medications, even at very high levels of poor adherence. Many healthcare providers tend to overestimate their patient's medication adherence[29].

A retrospective analysis of dosing histories of patients prescribed once a day AHT drugs showed that non-persistence is the leading problem with adherence: beside the fact that half of the patients stopped treatment within a year, 48% had at least one drug holiday a year and almost 95% of them missed at least a single dose a year; the better a patient executed the drug regimen, the more likely he/she was to persist with the prescribed dosing regimen[115]. Therefore, the persistence rate is an important element in determining the success of any long-term therapy. As mentioned, discontinuation of AHT therapy is associated with poor BP control[24,61,127].

Further, in pharmacy dispensing/claims database studies, it is usually not possible to determine whether discontinuation was prescriber-initiated or patient-initiated. Therapy or medication discontinuation in electronic database studies can only be assessed within the context of a pre-specified operational definition for the required number of days without medication available[101] that distinguishes this behaviour from non-adherence[84]. This period is known as the maximum 'allowed treatment gap' or 'grace period'[82,85;115].

Treatment discontinuation is typically defined as a gap of 30, 60 or 90 days or the time corresponding to two missed prescriptions between the end of 1 dispensed medication supply and any subsequent claim for the same medication[25,84-85,93]. A minimum of 60

days is generally used, because in many countries, many prescriptions include 30 days of supplied medication; 60 days without therapy would, therefore, indicate missing two adjacent prescriptions. If the standard duration of a prescription is different than 30 days, it is recommended to use the time corresponding to 2 missed prescriptions as the minimum period for treatment discontinuation. For this calculation, only the amount of medication dispensed in the prescription immediately preceding the 60-day period should be considered. Medication leftover from previous prescriptions (i.e. when refills are made before the end of the days supplied) should not be used in determining treatment discontinuation[84].

Variation of the allowed treatment gap has a large influence on persistence rates and the proportion of persistent patients is more stable at larger maximum allowed treatment gaps, although more stable does not imply better reflecting actual discontinuation. The relation between the maximum allowed treatments gaps and the duration of the prescription is meant to decrease misclassification based on the length of a prescription a patient is receiving. When the goal of the study is to study persistence with drugs and compare different drug classes with each other, the maximum allowed treatment gap should be large, at least 90 days or one time the theoretical duration of the last prescription[82]. Thus, very low measured levels of adherence can in some circumstances represent, or are confused with, discontinuation[101].

2.4. RISK FACTORS FOR MEDICATION NON-ADHERENCE

Medication-taking behaviour is extremely complex and individual, influenced by multiple factors, which requires numerous multi-factorial strategies to improve adherence to medications[17]. The published literature identifies hundreds of determinants of non-adherence. A recent review of systematic reviews identified 771 individual factor items associated with adherence to long-term treatment, the vast majority of which were determinants of implementation, and only 47 were found to be determinants of persistence with medication[128]. It is worth noting that this review, encountered difficulties due to the lack of standardized definitions, because many studies do not indicate the relative importance of the three elements of adherence to medications.

As discussed by the WHO in the report "*Adherence to long-term therapies: Evidence for action"*[11], factors contributing to lack of adherence and/or persistence can be divided in five categories: socioeconomic, condition-related, therapy-related, patient-related, and healthcare team and system-related factors.

2.4.1. Socioeconomic factors

Many reviews reported a positive effect of family and social support on adherence, and a negative effect of the lack of such support[128]. A meta-analysis of 122 studies, conducted by Scheurer et al[129], aimed at assessing which type of social support (practical, emotional or undifferentiated) had the strongest relationship with adherence, found that practical social support (i.e. supervision of medication administration by others) yielded significantly higher effects than emotional and undifferentiated support.

Economic factors such as unemployment, low income, poverty, lack of, or inadequate medical/prescription coverage, as well as high out-of-pocket costs of prescribed medications may seriously contribute to non-adherence[11;17;67;128;130].

One of the best documented barriers to adherence to medications is high out-of-pocket costs. Numerous studies have found that increased medication co-payments are associated with decreased use of prescribed medications, even for highly effective ones used to treat chronic conditions, such as hypertension[56;65-66;102;110-112;131-132].

Choudhry et al[132] found that the odds for full adherence to CV medications increase, even though modestly, by upward the coverage for medications.

However, the higher rate of adherence to ARBs compared with diuretics found in a meta-analysis on the impact of drug class on adherence to AHT, suggests that drug cost plays a relatively minor role in AHT adherence. The authors argue that it is possible that cost plays a more significant role in underinsured populations in which medication users are responsible for a significant portion of prescription costs[19]. Also, cost is less an issue now than in the past because many AHT drugs are available in generic form, which reduces its impact[13] because as Shrank et al[107] demonstrated, adherence is greater for generic drugs compared to brand name, and more expensive ones.

Shrank's[107] findings are not consensual and applicable to all conditions. Briesacher et al[131] found that although generic prescribing was associated with modestly improved adherence in some conditions (hypothyroidism and hypercholesterolemia), for hypertension it was associated with poorer adherence. Corrao et al[133] found that patients who started AHT therapy with generics did not experience a different risk of discontinuation compared with those starting on brand name agents.

Still, in Portugal a survey conducted for the *Spring Report 2013*[134], demonstrated that more than half of patients mentioned that have replaced their usual medications for less expensive ones; 13.3% stated to fully stop taking their medications and 15.8% mentioned that they have started to take less dosages, in order to hoard their medications. The authors of the report found that this was more common for statins, AHT and antidepressants.

2.4.2. Condition-related factors

Adherence relates to condition. Asymptomatic nature of the disease may reduce patient motivation to take their medications as prescribed, whereas disease severity may have a positive effect on adherence[56;67;128;130].

Adherence rates are rather low in preventive treatment and/or in conditions under which a long abstinence may not immediately be followed by serious consequences[93]. Previous studies have also demonstrated that adherence to medication continues to decline even after a stroke[17]; thus it is not surprising that treating asymptomatic conditions to prevent the possible occurrence of adverse events years later presents an even greater challenge.

Hypertension is largely asymptomatic, and patients often have a poor understanding or may lack awareness of the long-term consequences of elevated BP or the importance of BP control[11;17-18;35;66;127;130;135-136].

Additionally, many patients with hypertension remain free of symptoms after the onset of this chronic condition. However, treatment itself produces adverse effects in some

patients[56;66;127], and therefore, non-adherence has been reported to increase with any adverse effects and with increasing numbers of adverse effects (even with patients' perceptions of adverse effects[17]). Adverse effects like dry cough, dizziness, nausea, and headache associated with some AHT drugs may interfere with adherence, because patients weigh these immediate problems against the long-term benefits of treatment[127]. In a study performed in Portugal on medication adherence, patients' responses to the questionnaires showed that the main reasons for non-adherence related to the drugs themselves were adverse effects and symptomatic improvement followed by discontinuation[82].

This non-adherence to medications secondary to adverse effects is termed 'rational non-adherence', which Garner[137] defines as "the cessation of a prescribed therapy because of concern for, or the presence of, medication side effects". The author further states that rational non-adherence "is nearly impossible to circumvent if a patient's specific side-effect concerns are not substantially addressed". Therefore, it is critical that adverse effect profiles are considered when prescribing a medication and discussed with the patient before the initial prescription and at every visit thereafter[17].

Adherence to medication also involves adopting and maintaining medication-taking behaviours that may change the daily routine. Due to the lack of symptoms, treatment may not be perceived by the patient as absolutely necessary[67].

2.4.3. Therapy-related factors

If treatment is patient unfriendly, due to its complexity, the likelihood of patient adherence drops[11;26;56;63;66;112-113;138-141]. The complexity of the prescribed regimen consists of three major domains: the number of medications prescribed; the complexity of administration, and daily dosing frequency[142].

The need to take many different medications and/or the complexity of the prescribed regimen was the main reason for non-adherence in 8.7% of patients, in the study conducted by Cabral and Silva[82]. Even for those who did not indicate complexity of the therapy as the main reason for non-adherence, it was considered an important factor affecting adherence by over 40%.

Subsequently, the simplification of daily dosing frequency has a high potential to improve medication adherence in patients with hypertension[24;140]. Simplified dosing regimens can result in improvements on adherence to medications between 8% and almost 20%[50]. Several studies[22;62;66;68;89;138;140;143] have confirmed the inverse relationship between medication adherence and the prescribed number of doses per day, also in the hypertension setting as well. A meta-analysis including data from 11.485 patients demonstrated that the average adherence rate for QD dosing was significantly higher than for BID (twice a day) dosing in hypertension[142]. Another systematic review conducted in Portugal, showed that QD dosing vs. BID or higher dosing was associated with a reduction of 56% in risk of non-adherence to treatment[68].

In addition to the complexity of the therapeutic regimen, a longer duration of the treatment may also affect negatively adherence to medication[128;130;142]. The meta-analysis of Iskedjian et al[142] also demonstrated that, the longer the therapy lasted, the lower the adherence rates.

Polymedication, as in an excessive number of prescribed medications also as a negative effect on adherence due to the increased risk of toxic and/or adverse effects of medications[128;144].

Mazzaglia et al[63] observed improved adherence (≈30%) associated with combination therapy compared with monotherapy, which supports that the use of low-dose combinations favours adherence because of the smaller side effects compared to full-dose therapy[5;138]. The combination should preferably contain long-acting substances to maximize forgiveness against brief periods of dose omissions[50]. Studies have demonstrated that the use of single-pill combinations has some advantages. But it also has drawbacks. Indeed, if the patient omits several consecutive doses of a single-pill combination, he/she actually misses two or three drugs simultaneously, increasing the risk of hypertension rebound effects[97]. However, although single-pill combinations have been shown to improve execution or implementation, the impact on persistence is only modest, with a 10% to 20% improvement over 1 year[145].

Pharmacy refill and claims data suggest that there are differences in adherence among the most commonly prescribed AHT drug classes. Compared to ARB agents, ACEIs, and CCBs, thiazide diuretics, and BBs have increased gaps between prescription refills and are more likely to be discontinued[66;91], possibly due to increased adverse effects of medications from these classes[19;86;90;143]. Diuretics, for example, can cause urinary frequency, erectile dysfunction, fatigue and muscle cramps. They can also produce metabolic and electrolyte abnormalities that may lead physicians to discontinue those[19]. Adverse effects reported with ARBs are substantially lower than those reported for other classes of AHT[50].

Some studies have shown that persistence with AHT treatment depends largely on the choice of the initial drug class[59;66;91-92]. According to a recent meta-analysis, mean persistence to AHT medications was 65% for ARBs vs. only 28% and 51% for BBs and diuretics, respectively. The authors found a remarkable degree of consistency in the demonstration of superior adherence to ARBs and ACEIs and inferior adherence to diuretics and BBs[19]. The association between BB and non-adherence may also be likely explained by the increased propensity for the first to be prescribed as multiple doses per day[143]. Another possible explanation for the differences in adherence by drug class may be variation in provider and patient beliefs about medications[19].

2.4.4. Patient-related factors

Several patient-related factors, including lack of understanding of their disease, lack of involvement in the treatment decision-making process, and suboptimal health literacy, contribute to medication non-adherence[17;56;128].

A recent systematic review and meta-analysis of epidemiological studies demonstrated that a low health literacy is one of the factors which significantly influence adherence levels (in a subset of studies with relevant information), a long side with low social status[56]. Also, higher income has small yet positive effects on adherence[146].

As mentioned, patients may have a poor understanding or may lack awareness of the long-term consequences of elevated BP or the importance of BP control, particularly because hypertension is often asymptomatic (e.g. no immediate physical symptoms

resulting from missing doses, on either an occasional or permanent basis, are apparent)[11;17-18;35;127;130;136]. However, inadequate health literacy is often under recognized and therefore not addressed by healthcare providers[17].

Lack of awareness may be particularly relevant for newly diagnosed hypertensive patients, who generally have lower persistence rates than patients with established hypertension[27]. Patient's awareness of their adherence patterns can change their medication-taking behaviour. A review and meta-analysis of adherence enhancing interventions in 79 RCT, showed that feedback to patients about their medication-taking patterns was the biggest factor influencing adherence[147].

The patient's health beliefs and attitudes concerning the effectiveness of the treatment, such as beliefs about the efficacy of treatment; "being tired" of taking medications and/or perceived excessive medication use; their previous experiences with pharmacological therapies, and lack of motivation also affect the degree of adherence to medication[11;17]. A belief that the medical condition in question was a threat because of its severity may increase adherence[128].

Within this context, a key component of any adherence-improvement plan should be patient education. The more empowered patients feel, the more likely they are to be motivated to manage their disease and adhere to their medication. Thus, actively involving patients in treatment decisions when possible is also a factor to consider[17].

Several determinants, including age and gender are known to be associated with discontinuation of AHT therapy[66;85-86]. Older patients tend to continue longer treatment than younger patients and male patients tend to show more persistence than female patients[66]. However, age and gender were found to have an inconsistent impact on the implementation of correct dosing[128].

2.4.5. Healthcare team and system-related factors

Inefficient health systems, with insufficient distribution of medication, lack of knowledge and education of healthcare professionals regarding specific chronic diseases, the limited time for consultation and availability for follow-up, lack of

incentives, the inability to evaluate patient's level of adherence to medications and its impact on health indicators, are of paramount importance and interfere with adherence to prescribed therapies[67].

Not only do physicians often fail to recognize medication non-adherence in their patients, they may also contribute to it by prescribing complex drug regimens, failing to explain the benefits and adverse effects of a medication effectively, and inadequately considering the financial burden to the patient[17;23]. Ineffective communication between the physician and the patient with a chronic disease such as hypertension further compromises the patients understanding of his or her disease, its potential complications, and the importance of adherence to medication[17].

The substantially improved adherence of patients who report a good relationship with their physician highlights the important role of physicians in the medication adherence process[23;148-151]. The risk of nonadherence is 19% higher in patients whose physician communicates poorly compared with patients whose physician communicates well[148]. Healthcare provider's ability to demonstrate empathy has a positive effect on adherence to medication[130;149] because it promotes trust and respect and enhances motivation of patients to take medications[13]. Persistence rates are directly correlated with a strong and trusting physician-patient relationship[66].

By asking the appropriate questions, physicians can accurately access which medications patients are taking and how they are taking them[17;149]. Questions such as[17]:

i. I know it must be difficult to take all your medications regularly. How often do you miss taking them?
ii. Of the medications prescribed to you, which ones are you taking?
iii. Of the medications you listed, which ones are you taking?
iv. Have you had to stop any of your medications for any reason?
v. Have you noticed any adverse effects from your medications?

However, physicians often do not ask about medication adherence. Lack of time, doubt that low adherence is a cause of uncontrolled BP, and uncertainty about how accurately determine adherence and use this information in clinical practice are some of the

limiting factors for physicians considering adherence in their clinical decision-making[150].

Different studies[35;151] have demonstrated that medication adherence is the most likely independent variable to be positively influenced by an healthcare professional, in order to improve BP control.

Another healthcare team factor that may influence adherence to medication is the number of prescribers involved in the management of chronic diseases, such as hypertension. Barat et al[152] found that the risk of non-adherence increased when patients get prescriptions from more than one prescriber.

CHAPTER 3: QUANTIFICATION OF ADHERENCE TO MEDICATIONS

An appropriate quantification of adherence to medications constitutes the basis for adherence-related sciences, by informing the process of managing adherence, the aim of which is to help patients to take appropriately prescribed drug dosing regimens[25].

It should be made by using a clear and precise taxonomy and provide meaningful metrics which should be reliable, allow tracking over time, be coherent with the three elements of medication adherence and be implementable on a large scale[122]. It is well known that adherence to medications is often misclassified and poorly quantified, and that can lead to both erroneous conclusions regarding the efficacy of treatments as well to dose-response relationships which will ultimately impact on patient care with serious adverse consequences on patient care[153]. The ultimate goal is optimal pharmacotherapy and its implicit association with optimal clinical outcomes[25].

Although rates of adherence for individual patients are usually reported as the percentage of the prescribed doses of the medication actually taken by the patient over a specified period of time[23;26], the difference introduced by the construct of medication adherence as a dynamic process precludes a single, quantitatively useful parameter to cover all three components. Previous studies have shown major differences in the dynamics of the three components of adherence to medications over time, which can reveal different causes and/or consequences[25].

The majority of studies tend to employ indirect measures of adherence and categorize the medication use during the course of therapy into either "good" or "poor" levels of adherence[30;56]. On hypertension studies, a threshold value of 80% is commonly used[23-24;26;56;91;111;129;137-138;141;153], which is close to the average adherence value, 76%, reported by Cramer[68] across several studies of AHT drugs and has been accepted as the most conventional and widely reported cut-off for optimum adherence[55].

Still, some authors argue that setting arbitrary cut-offs, such as 80%, are sometimes of little clinical interest for many reasons. One of them is that an adherence of 80% can be achieved in many different ways, each with a very different clinical impact (*e.g.*, one missed dose every five days or one missed week of doses every five weeks).

Vrijens, Urquhart and White[72] have demonstrate that using data collected electronically during a three-month period for patients prescribed with BID doses. Figure 2 shows drug dosing histories for four patients, each of whom took 75% of their prescribed drugs during the three-month period. The blue dots represent taken doses and vertical grey bars represent omitted doses. The first three patients display partial implementation: (A) patient mainly missed evening doses; (B) patient missed both evening and morning doses; (C) patient display a drug holiday; (D) patient initially had a high level of adherence, but discontinued therapy prematurely.

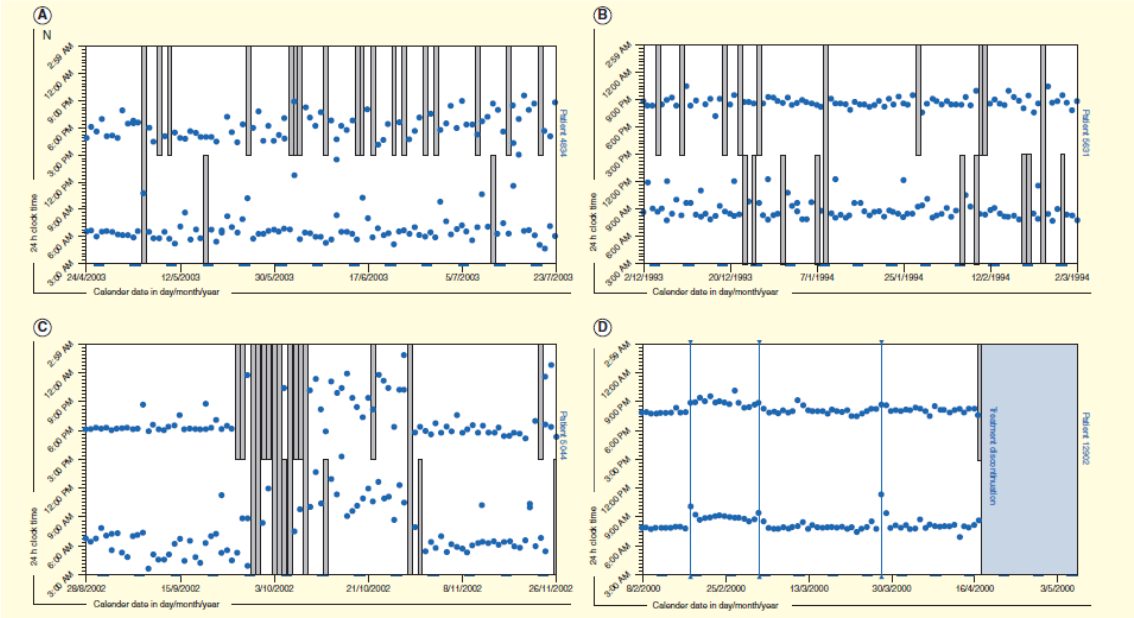

Figure 2. Differences in adherence patterns (figure from Vrijens, Urquhart and White[71])

Furthermore, no one really knows what level of adherence is sufficient to obtain the full benefit of a medication because medications were rarely investigated in this respect. Thus, depending on the pharmacological characteristics of the prescribed drug, 80% of prescribed doses taken may be sufficient or not for full therapeutic benefit[97].

There are many different methods for measuring adherence to medications. Osterberg and Blaschke[23] categorized these methods as either direct or indirect (Table 2).

Table 2. Methods of measuring adherence to medications

METHOD	ADVANTAGES	DISADVANTAGES
Direct methods		
Directly observed therapy	Most accurate	Patients can hide pills in the mouth and then discard them; impractical for routine use
Measurement of the level of medicine or metabolite in the blood	Objective	Variations in metabolism and "white-coat adherence" can give a false impression of adherence; expensive method
Measurement of the biological marker in blood	Objective; in RCT can be used to measure placebo	Requires expensive quantitative assays and collection of bodily fluids
Indirect methods		
Patient questionnaires; patient self-reports	Simple; inexpensive; the most useful method in clinical setting	Susceptible to error with increases in time between visits; easily distorted by patients
Pill counts	Objective, quantifiable, and easy to perform	Data easily altered by the patient (e.g. pill dumping)
Rates of prescription refills	Objective; easy to obtain data	A prescription refill is not equivalent to ingestion of medication; requires a closed pharmacy system
Assessment of the patient's clinical response	Simple; generally easy to perform	Other factors besides medication adherence can affect clinical response
Electronic medication monitors	Precise; results are easily quantified; tracks patterns of taking medication	Expensive; requires return visits and downloading data from medication vials
Measurement of physiological markers	Often easy to perform	Marker may be absent for other reasons (e.g. increased metabolism, poor absorption)
Patient diaries	Help to correct for poor recall	Easily altered by the patient

Adapted from Osterberg and Blaschke[23]

Although direct methods are considered to be more robust than indirect methods, they also have some limitations. All these methods differ with regard to their validity, reliability and sensitivity[23] and none of them provide 100% robust data[60;74].

Also what is 'measured' is not the same in every method. Rates of prescription refills, for instance, measure medication acquisition, which is different than medication consumption, measured by pill counts, physiological markers, or electronic medication monitors[30].

Much effort has gone into devising methods for reliably quantifying ambulatory patients' adherence to prescribed medications, especially those intended for long-term use against various major chronic diseases[25].

The best of the available methods provide for the reliable capture, storage, analysis, and communication of dosing history data in ways that make it difficult or impossible for patients or trial staff to censor or otherwise manipulate the data. Methods that meet these criteria include the following: (1) retrospective analysis of prescription refill records (i.e. pharmacy refill rates), (2) analysis of chemical markers of drug exposure, such as the level of the medicine or its metabolite in the blood and (3) electronic medication monitors with automatic electronic time-stamping and compilation of events more or less strongly linked to the act of medication-taking (e.g., package opening, dosage form dissolution)[29;115].

Other methods, such as questionnaires, interviews, and periodic counts of patients' returned, untaken doses, are subject to many uncertainties and easy manipulation by patients[25]. Electronic monitoring of adherence, for instance, has shown that pill counts overestimate medication consumption[30]. A recently published paper also demonstrated that objective urinary drug levels quantification by liquid chromatography mass spectrometry does not overlap with questionnaire results. An objective quantification of adherence shows a higher rate of non-adherent patients[155].

Until recently there was no scientific justification to considerer one of these as the 'gold standard'[23;74]. Electronic methods for compiling drug dosing histories have emerged as

the currently recognized standard for quantifying adherence[72] even though its utilization is not widespread, especially due to the costs associated and its potential for patients to manipulate the device[125].

Although electronic monitoring of adherence increases measurement accuracy, in the context of implementation[24], for evaluation of initiation and implementation in real world conditions, prescription and refill databases are the best method[122] (Table 3).

Table 3: Advantages and disadvantages of methods of measuring adherence to medications

	INITIATION	IMPLEMENTATION	DISCONTINUATION
Self-report	Desirability bias	Recall bias	Desirability bias
Pill counts	Easily censored by patient	Only aggregate summary	Easily censored by patient
Direct methods (PK/PD)	Requires sampling after prescription	Sampling is too sparse	Subject to 'white-coat adherence'
Prescription and refill databases	Gold standard if both databases are combined	Only aggregate summary	Gold standard but retrospective
Electronic monitoring	Gold standard in clinical trials needs activation	Gold standard	Gold standard in clinical trials needs patient engagement

Adapted from Vrijens and Heidbuchel[118]

Legend: PK/PD – pharmacokinetics/pharmacodynamics

3.1. RATES OF PRESCRIPTION REFILLS

As mentioned, rates of pharmacy refill, extracted from pharmacy dispensing/claims databases, can be used as a surrogate for adherence to medications, since they reflect patients' decision to continue with their prescribed therapy and patients' effort to obtain the medication as the first step toward taking it[34]. By assessing whether patients acquire (e.g. fill) their medications over specified time intervals, they allow the evaluation of the medication-acquisition behaviours[30;34].

Pharmacy dispensing/claims databases have several known advantages: (1) they are not subject to memory bias[156-157]; (2) data access and collection is done electronically[31;33;85] and therefore, in a relatively easy manner[67;85]; (3) it's accuracy is high[33]; (4) lower costs compared to other methods[33;67;85;157]; (5) large populations of patients can be followed over long periods of time[31;67]; (6) it's not required any informed consent from individuals for data collection[32], because studies can be accomplished with de-identification of patients[158-159], thus protecting their privacy[31;33;157].

However, such databases also have some disadvantages: (1) prescription records aren't always reflected in claims records; (2) dispensing does not necessarily means actual use[33;156;159]; (3) the duration of use can't always be predicted from package size or theoretical dosage regimen[156]; (4) missing information on over-the-counter medication[33;156;159], self-medication[156] and drugs dispensed in hospitals[33]; (5) data sources not designed for research[31]; (6) the information on individuals is usually sparse[33] – missing data elements, unmeasured confounders and data quality and integrity may not be the same across the database, namely by misclassification of drug exposure and/or outcomes or even diagnostic misclassification[31].

Within such limitations, refill rates cannot clearly determine whether a patient does not adhere to their prescribed medications because he or she has not followed up with the provider to receive a new prescription, the provider has not written the prescription, the prescription was written but not delivered to the pharmacy, or the prescription was delivered to the pharmacy but not fully picked up (i.e. prescription for two packages but only one was acquired by the patient)[107].

Although the use of pharmacy dispensing/claims databases has a number of limitations, its relative efficiency for studies of adherence and persistence in large populations in a real-world setting is highly advantageous[23;26;67;109].

Prescription refill records are only a valid source of information about medication-taking behaviour when the database is complete; if the patient uses a pharmacy not linked to the database, then it can lead to incomplete and erroneous calculations[18]. If that's not the case and patients are unlikely to obtain the medications from other sources not captured by the database, the estimates derived from studies using automated data,

can be considered to have a high specificity, e.g. identify those not consuming the medications[18;23;26;30;100].

3.2. METRICS USED TO CALCULATE MEDICATION ADHERENCE AND PERSISTENCE

In general, the metrics that have been used to calculate medication adherence and/or persistence enable calculation of either medication possession (i.e., possession measures) or gaps in medications availability (i.e., gap measures)[26;160-162] and most estimate adherence only among individuals with secondary adherence, as previously mentioned. Table 4 displays different medication adherence measures that have been used in studies with pharmacy refills.

Most metrics are continuous measures, but they are often categorized (e.g., low or inadequate versus moderate versus high or adequate adherence)[23-24;26;30;56;91;105;131;139-140;143;152-153].

These measures require data including the date of medication dispensing, days' supply dispensed with each dispensing, and previous (stockpiled) medications (or an indication that it will be set to zero) to estimate medication availability and consumption. The metrics also vary in whether or not the days' supply dispensed with the terminal dispensing is included in the calculation. The time between any one dispensing and the subsequent dispensing is known as the refill interval. Person-time is censored at the last dispensing date, at the time of exhaustion of the last days' supply, or at a fixed number of days after exhaustion of the last days' supply. Most gap measures of secondary adherence censor after the last dispensing once stockpiled medications have been exhausted[30;101].

The assumption beneath the maximum medication gap is that these gaps are due to reduced adherence rather than to clinicians' instructions for temporary or permanent drug cessation, or to acquisition of medications outside the pharmacy system[30].

Table 4. Adherence measures reported in pharmacy refill studies

MEASURE	FORMULA	VALUE	TYPE
CMA Continuous Measures of Medication Acquisition	cumulative days' supply of medication obtained / total days to next fill or to end of observation period	adherence value for cumulative time period	medication availability
CMG Continuous Measure of Medication Gaps	total days of medication gaps / total days to next fill or end of observation period	non-adherence value for cumulative period, censored at zero	based upon medication gaps
CMOS Continuous Multiple Interval Measure of Oversupply	(total days of medication gaps - leftovers) / total days in observation period	non-adherence value for cumulative period, allowing for leftovers	based upon medication gaps
CSA Continuous, Single interval measure of Medication Acquisition	days' supply obtained at beginning of interval / days in interval	adherence value for interval of study participation	medication availability
MPR Medication Possession Ratio	days' supply / days in period	ratio of medication available	medication availability
PDC Proportion of Days Covered	(total days' supply/total number of days evaluated) x100, capped at 1.0	percentage of days with medication available	medication availability
RCR Refill Compliance Rate	[sum of quantity dispensed over interval / quantity to be taken per day) x100] / number of days in interval between first and last refill	overall adherence percentage	medication availability
GAP	total days of the maximum medication gap / total days in observation period	non-adherence value for cumulative period	based upon medication gaps

Adapted from Andrade[23], Steiner and Prochazka[30] and Vink[162]

The most frequent statistics used for quantifying, within a patient, the implementation of a dosing regimen, over a defined period of time, are: (1) the proportion of prescribed drug taken; (2) the proportion of days with the correct number of doses taken; (3) the proportion of doses taken on time, in relation to a prescription-defined time interval between successive doses; (4) the distribution of inter-dose intervals; (5) the number of drug holidays; and (6) the longest interval between two doses[25].

Within such statistics, the two most commonly used secondary adherence medication possession measures are the Medication Possession Ratio (MPR) and the Proportion of Days Covered (PDC)[26,84,100,160-162]. Both report medication availability by estimating the proportion of prescribed days' supply obtained during a specified observation period over refill intervals. Both MPR and PDC correlate well with the quantity of doses taken but not with the timing of the doses, and the quantification of adherence with these metrics is more difficult when the length of follow-up varies between patients[100].

The main difference between the PDC and the MPR is that with the PDC any oversupply is truncated, whereas adherence values of greater than 100 percent are allowed with the MPR. There is controversy about whether 'over adherence', often considered as MPR between 100 and 120 percent, has clinical meaning[101]. Although a MPR over 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 AHT drugs at greater than the prescribed frequency. Therefore, MPR should also be capped at 100%[26].

The systematic review conducted by Andrade et al[26] demonstrated that within the majority of studies, MPR is estimated as the day's supply of medication dispensed during a specific follow-up period (e.g. one year) divided by the number of days from the first dispensing to the end of the follow-up period.

Many pharmacy dispensing/claims databases do not provide information on days supplied for prescriptions but do include amount dispensed; to determine MPR or PDC, the number of pills dispensed and doses per day (either from the database or from standard medication references) can be used to estimate the number of days supplied[26,84].

Several limitations to MPR calculations are related to the nature of retrospective databases. For example, patients may obtain the medication(s) of interest from sources not captured in the available data, such as sharing medication with others (e.g. family members). The main limitation to MPR calculations (i.e. not related to retrospective data) is the assumption that the proportion of days covered by a prescription corresponds to the proportion of days of medication use. Patients may fill prescriptions at regular intervals yet not take the medication in the manner prescribed. Nevertheless, MPR is the accepted standard for the evaluation of adherence using retrospective data; it's easy to calculate, it's a well-established objective measure of pharmacy refill adherence and is the most commonly used metric, allowing for comparisons among studies. Therefore, MPR is the best available measure for assessing adherence to AHT medications using retrospective data[34].

In terms of persistence, Caetano et al[163] identified five different methods for calculating persistence: anniversary models, minimum-refills models, refill-sequence models, proportion-of-days-covered models, and hybrid models. When these models were applied to data for a hypothetical patient, a wide range of values and interpretations resulting in a total persistence with drug therapy ranged from 7 days to >1 year. The authors stated that a standard operational definition of persistence should be bi-dimensional, quantifying not only the total duration of therapy, but also the intensity of medication-taking within this interval.

CHAPTER 4: OBJECTIVES

GENERAL OBJECTIVE

The main objective of this thesis is to determine adherence to antihypertensive therapy in newly diagnosed and treated hypertensive patients in Primary Health Care units of Lisbon and Tagus Valley Health Region.

SPECIFIC OBJECTIVES (PRIMARY):

i. Determine the rate of primary adherence to prescribed AHT drugs;
ii. Determine the rate of initiation of AHT therapy;
iii. Determine the rate of implementation of AHT therapy in the observation period;
iv. Determine the rate of two-year persistence to AHT therapy.

SPECIFIC AIMS (SECONDARY):

i. Identify risk factors for non-initiation of AHT therapy;
ii. Identify risk factors for poor quality of implementation of AHT therapy;
iii. Identify risk factors for discontinuation of AHT therapy.

CHAPTER 5: RESEARCH METHODS

5.1. LOCAL CONTEXT

Data analysed in this thesis were collected from the information system of the Regional Health Administration of Lisbon and Tagus Valley (ARSLVT). Lisbon and Tagus Valley Region is a region of Portugal which accounts for about 13% of the Portuguese territory and 34.6% (3.7 million) of its population[164].

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[165]. In spite of that, the costs with reimbursement of prescribed drugs of voluntary private and public health insurance in Portugal have been decreasing over the last years, representing in 2011, less than 12.5% of the NHS total costs with reimbursement of prescribed drugs[166].

Electronic prescribing is mandatory for all NHS reimbursed drugs regardless the health care providing system since 2010[167]. A report from the Portuguese Ministry of Health (data of the period between February 2011 and June 2012) shows 98.7% of electronic ambulatory prescriptions in the PHC sector; 97.7% in public hospitals and 73.7% in private practice[168].

Drug prescriptions 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 prescriptions information is collected centrally by the NHS[169]. However, since the inclusion of the dosage regimen is not mandatory for prescription validation, that specific information is not always registered.

For acute situations, drug prescriptions are valid for a 30-day period after the date of the 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[169].

Community pharmacies then submit electronic claims for reimbursement of the NHS and/or voluntary private and public health insurance funded components of dispensed drugs to a centralized reimbursement system, in functions since March 1st, 2010. All reimbursed drugs are registered here[170].

For AHT drugs – the focus of this thesis – reimbursement corresponds to 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[171].

The linkage between prescriptions and dispensing/claims data can be made through the information system of the Regional Health Administration – SIARS, which is an administrative database, developed to facilitate analysis and monitoring PHC units' activity and production. This automated system includes information on diagnosis made and registered at PHC units, as well patients' demographic and administrative data.

5.2. STUDY DESIGN

We've conducted an observational study, more specifically a retrospective cohort study. We used a cohort of newly diagnosed and treated hypertensive patients, within the PHC units of Lisbon and Tagus Valley Region. We identified all patients – aged between 18-90 years – who were diagnosed with hypertension and received a first prescription (*index prescription*) for at least one AHT drug during the first trimester of 2011 - Jan 1st to Mar 31st.

Hypertension was defined in the terms of codes k86 - Hypertension uncomplicated – and k87 – hypertension complicated – of the International Classification of Primary Care, 2nd ed. (ICPC-2)[172].

AHT drug classes for which the several adherence rates were determined, with corresponding anatomical therapeutic chemical (ATC) classification system codes were:

- C02: Antihypertensives
    - C02A: antiadrenergic agents, centrally acting

    - C02C: antiadrenergic agents, peripherally acting
- C03: Diuretics
    - C03B: low-ceiling diuretics, excl. thiazides
    - C03C: high-ceiling diuretics
    - C03D: potassium-sparing agents
    - C03E: diuretics and potassium-sparing agents in combination
- C07: Beta blocking agents
    - C07A: beta blocking agents
- C08: Calcium channel blockers
    - C08C: selective calcium channel blockers with mainly vascular effects
    - C08D: selective calcium channel blockers with direct cardiac effects
- C09: Agents acting on the renin-angiotensin system
    - C09A: ACE inhibitors, plain
    - C09B: ACE inhibitors, combinations
    - C09C: angiotensin II antagonists, plains
    - C09D: angiotensin II antagonists, combinations
    - C09X: other agents acting on the renin-angiotensin system.

Within each class, only drugs indicated for the treatment of hypertension (as expressed by each Summary of Product Characteristics – SmPC) were analysed.

Prescriptions and claims (drugs dispensed with a prescription) data of AHT drugs were collected for every patient for a two-year follow-up period after *index date*, i.e. the date of first acquisition of at least one AHT drug in a community pharmacy.

5.3. STUDY POPULATION

Study population consisted of all patients diagnosed with hypertension and newly treated for that condition during the first trimester of 2011 in the PHC units of Lisbon and Tagus Valley Region, with no prior use of AHT drugs until January 1st 2011.

To determine whether patients were truly new users of AHT therapy, prescriptions and claims data were collected additionally for a period of 6 months prior to January 1st

2011. Therefore, patients with no prescriptions and/or no claims records for any AHT drug in the 6-month period before January 1st 2011 were classified as newly treated patients (new users), whereas those who received prescriptions for AHT drugs in this run-in period were classified as established users and weren't include in the cohort.

5.3.1. Exclusion criteria

- Patients outside the defined age range (18-90 years).
- Patients with at least one prescription and/or claim record prior to Jan 1st 2011, i.e. established users.
- Patients with an index date prior to the index prescription (an index date prior to the index prescription makes it impossible to determine time to initiation).

5.4. EXPOSURE DEFINITIONS AND ADHERENCE MEASURES

Exposure to AHT therapy was defined as the duration of all dispensings of AHT drugs, per patient, within the observation period, starting from *initiation* (set by the index date) and ending at *discontinuation* or the end of the observation period, whichever occurred first.

5.4.1. Rate of primary adherence

The rate of primary adherence was expressed as the number of claims records divided by the total number of prescriptions records. This was done considering that each claim corresponds to a single AHT drug package.

Primary adherence rate reflects only patients' acquisition of prescribed AHT drugs[26,102], meaning that a prescribed drug was dispensed within the legal defined number of days after it was prescribed.

By opposition, primary non-adherence was defined as the absence of a claim record for a prescribed AHT drug[102].

We compared primary adherence rates across patients' characteristics, such as gender, age, region, buying power and ICPC-2 code of diagnosis, as well across drug classes and other drug characteristics, such as its classification as generic or brand name drug and out-of-pocket costs.

Bivariate analysis was conducted to determine which characteristics were related to primary adherence. Categorical variables were analysed using the chi-square test.

5.4.2. Initiation

In this thesis, initiation was evaluated as a dichotomous event (patient initiates therapy: yes/no) but also as a time-to-event variable.

In the first analysis, initiation was quantified as the proportion of patients not exceeding the six-month period after index prescription (i.e. new users of AHT therapy), which is the maximum allowed period of time for dispensing of a prescribed drug in a community pharmacy in Portugal[169].

In the second analysis, time to initiation (time-to-event variable) was defined as the length of time from index prescription (time origin) to index date (end-point) within the six-month period after index prescription. The index date was used as a proxy for first dose taken[25].

Initiation of treatment was analysed by Kaplan-Meier survival analysis, determining the time to initiation for each patient. Patients were censored six-months after the index prescription. Estimates of time to initiation were assessed for the potential predictors of initiation of treatment including age, gender, and pharmacological class, number of drugs initially prescribed, patients' buying power, ICPC-2 code and out-of-pocket costs of the prescribed AHT drugs.

Cox proportional hazard regression (including all potential predictors mentioned above) was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for initiation. The significance threshold was set at 0.05.

5.4.3. Implementation

Implementation was defined as the extent to which a patient's actual dosing regimen corresponded to the prescribed dosing regimen[25], throughout the two-year observation period.

Implementation was quantified by estimation of MPR per drug and per patient. This metric reports medication availability by estimating the proportion of days' supply obtained from community pharmacies during a specified observation period and in this thesis it was expressed by:

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

where the observation period refers to the period from index date to 731 days afterwards.

Since during the observation period, many changes to the initially prescribed treatment occurred, the formula for MPR estimation needed to be adjusted to different situations. So, when a new AHT drug was prescribed during the observation period subsequent to the index date – in addition to or in substitution of the first drug prescribed – a shorter denominator was used (starting from the date of the first dispensing for that new drug):

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

In the case of additions of new AHT drug(s) to the initially prescribed one(s), no changes were made to the formula for MPR estimation of the first drugs. However, in the case of substitution or switching[iii], the denominator of the first drug prescribed (and that was discontinued) was adjusted as follows:

[iii] We've considered substitution or switching in terms of complete discontinuation of one AHT drug with initiation of a new drug, regardless when that occurred.

$$(c)\ MPR = \frac{\text{number of days supply obtained during observation period}}{\text{number of days between first dispensing date and discontinuation date}} \text{ x } 100$$

being the discontinuation date, the date of the last dispensing of the initially prescribed drug or the index date of the new AHT drug, whichever occurs later.

Figure 3 shows the different scenarios for MPR estimation.

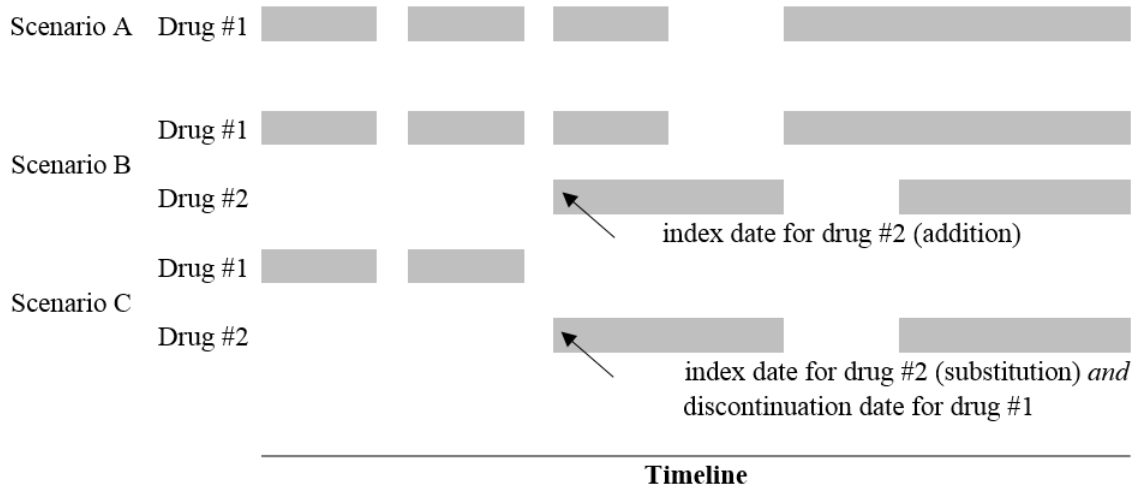

Figure 3. Different scenarios for MPR estimation

In scenario A, MPR is calculated only for a single AHT drug, using formula (a). In scenario B, MPR for drug #1 is calculated using formula (a) being formula (b) used for drug #2 (b) – the arrow marks the index date for drug #2. In scenario C, MPR for drug #1 is calculated using formula (c) being formula (b) used for drug #2 (b) – the arrow marks the index date for drug #2 and the discontinuation date for drug #1.

For patients receiving multiple AHT drugs, the MPR was estimated for each drug separately, and the overall MPR per patient was the mean of the individual MPR values.

Patients were then categorized in three levels of implementation or execution, accordingly to their estimated MPR: low (<40%); intermediate ([40-80[%) and high (≥80%) implementation. Afterwards, a threshold of 80% was used to dichotomize between good implementation and poor implementation (usually expressed in the literature as adherent *vs* non-adherent patients).

Calculations of MPR greater than 100% were set to 100%, because even though a MPR >100% may reflect patients refilling prescriptions before the end of their last dispensing or hoarding medication for later use, it is unlikely that patients will actually use AHT drugs at greater than the prescribed frequency[30].

Logistic regression was used to estimate the odds ratio (OR), with 95% CI, for poor implementation of the prescribed AHT therapy. Bivariate analysis was conducted to determine which characteristics were related to implementation. Categorical variables were analysed using chi-square test. The model was adjusted for age, gender, patient's buying power, number of AHT drugs dispensed during follow-up, and number of prescribers.

5.4.4. Discontinuation

Discontinuation marks the end of therapy, allowing the estimation of *persistence*[18,25]. Persistence, like initiation, is a time-to-event variable with a well-defined time origin (initiation) and an end-point which is the date of treatment discontinuation[25,84].

In this thesis, persistence was considered in terms of therapy persistence[84], i.e. the proportion of patients remaining on any AHT drug regardless of switching or the use of multiple drugs during follow-up.

Starting from index date, all dispensed prescriptions were considered uninterrupted if time between the end of one dispensing and the beginning of the following – maximum allowed treatment gap or grace period - was lower than 90 days. The discontinuation date was set as the end date of the dispensing previous to the first treatment gap of 90 days or longer.

If the discontinuation date was not observed during the observation period, the patient was classified as a continuous user, i.e. persistent. This allowed increasing specificity in detecting discontinuers' or non-persistent patients.

In a second analysis of persistence, we've considered just the theoretical end date of the last dispensing, regardless the AHT drug and the previous occurrences of treatment

gaps, as the discontinuation date. By doing so, we've analysed *reinitiation* of AHT therapy[115].

In both situations, persistence to AHT therapy was analysed by Kaplan-Meier survival analysis, determining the time to discontinuation for each patient. Patients were censored at the end of the follow up. Estimates of time to discontinuation were assessed for the potential predictors of persistence including age, gender, pharmacological class, number of drugs during the observation period, number of prescribers during the observation period, patient's buying power, and ICPC-2 code.

Cox proportional hazard regression was used to estimate HR and 95% CI for discontinuation, i.e., the proportion of patients not being persistent with treatment after two years. The significance threshold was set at 0.05.

Since several studies on adherence to medications have demonstrated that many patients interrupt their treatment, shortly after the acquisition in a pharmacy of their first prescription[11], phenomena called early discontinuation or short persistence[29;109], in this thesis we've also analysed the rate and characteristics related to early discontinuation, defined as the fail to ever refill, i.e. a patient acquired only his/her first prescription.

5.5. NUMBER OF DAYS' SUPPLY IN EACH PRESCRIPTION

To determine implementation and discontinuation, we had to consider a number of days' supply obtained in each dispensing, e.g. the duration of a dispensing. Since SIARS does not include information about the recommended or individual dosage regimen for all prescribed drugs, the (theoretical) duration of a dispensing was estimated in consideration to the number of units per package and the standard dosing for each AHT drug related to hypertension as a proxy of the prescribed daily dose (PDD).

Standard dosing – the maintenance dose, in adults – was retrieved from the SmPC of each AHT drug from INFARMED's (National Authority of Medicines and Health Products) website. When the SmPC was not available in Portuguese, EMA's (European Agency of Medicines) website was searched.

Since the standard dosing for each AHT drug may vary, we've defined it as following:

- Standard dosing *per se* (e.g. one tablet per day or one tablet twice a day, with no exceptions);
- In cases of up- or down-titration, if the number of doses is not modified over time, it remained unchanged (e.g. ramipril dose can be doubled at interval of two to four weeks to progressively achieve target BP; maximum: 10mg daily. Usually the dose is administered QD);
- In cases of dosing range, we've considered the lowest dose (e.g. felodipine 5mg tablets may be 1 tablet QD or 1 tablet BID; we've considered 1 tablet QD to increase specificity.

The appropriateness to clinical practice of the standard dosing, as extracted from SmPC, was evaluated by a panel of 30 physicians, including general practitioners, cardiologists and internists, in a ratio of 4:1:1. We've analysed the agreement for the standard dosing and the usual prescribing practice of each physician, as well the agreement between physicians, using the methodology expressed in Figure 4. Agreement's analysis was conducted using the kappa test.

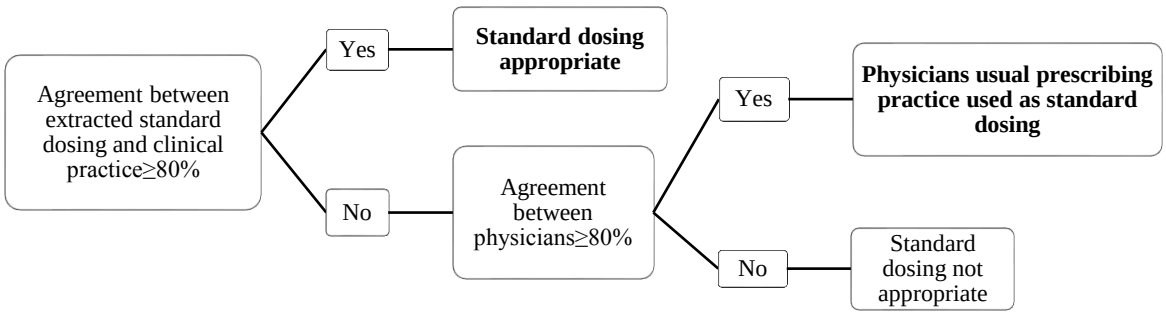

Figure 4. Flow chart for the analysis of the appropriateness of the defined standard dosing

Only for 3.7% of all dispensed AHT drugs, the defined standard dosing was not considered appropriate to clinical practice[173]. For those cases, and since in all of them the drug's dosing is defined within a dosing range, we've defined the standard dosing as

the lowest dose. By doing so, we've increase specificity in implementation and discontinuation analysis.

Taking into consideration the number of units per package and the defined standard dosing for each AHT drug related to hypertension as a proxy of the PDD, the end date of a dispensing equals its start date plus the duration of the dispensing. In case of overlapping dispensings, the second prescription was shifted forward to account for drug stockpiling.

5.6. DATA COLLECTION AND LINKAGE

As mentioned, data was collected from SIARS. In order to preserve privacy, data were collected and de-identified using encryption protocols, after which were provided to the research team by employees of ARSLVT, according to defined specifications in a variables codebook, which was previously discussed with ARSLVT leaders. Therefore, we were not be directly involved in data collection.

For each patient, prescription and dispensing/claims data were linked together using the unique prescription identification number. However, since each prescription can include up to four different drugs and therefore, patients may not acquire all prescribed drugs, we've also used the ATC code to match both files. Thus, a drug was defined as dispensed if there was a match between claims and prescribing records for the prescription individual identification number and the ATC code.

Linkage to patient's demographic data was done using patient's NHS number (*dummy* number).

5.7. STUDY VARIABLES

Table 5 presents study variables.

Table 5. Study variables

Variables for patient characterization		
Variable	**Categories (if applicable)**	**Source**
Age	continuous (years) categorical: 18-44; 45-64; ≥65	extracted from SIARS determined
Gender	male/female	extracted from SIARS
ICPC-2 code	k86/k87	extracted from SIARS
Housing parish code	used for determining patients' buying power and Region	extracted from SIARS
Buying power	categorical: <100;100-199; ≥200	extracted from Pordata
Region (NUTS III)	Great Lisbon, Setubal Peninsula, Middle Tagus, West, Leziria West Coast	determined using patient's housing parish code
Variables for prescriber characterization		
Variable	**Categories (if applicable)**	**Source**
Prescriber assigned to the patient	yes/no	extracted from SIARS
Variables for prescription characterization		
Variable	**Categories (if applicable)**	**Source**
Date of prescription		extracted from SIARS
(Data per drug): ATC code Drug class Brand/Generic name Strenght Number of packages Units per package RRP / reference price Cost for the NHS Cost for patient	 ATC code – 5th level Diuretics, BBs, CCBs, ACEIs, ARBs, Other AHT (ATC code – 2nd level) minimum: 1; maximum: 6	extracted from SIARS determined using ATC code

Legend: SIARS – Information System of the Regional Health Administration; ICPC-2 – International Classification of Primary Care, 2nd edition; NUTS – Nomenclatura das Unidades Territoriais para Fins Estatísticos; ATC code - Anatomical Therapeutic Chemical code; BBs – Beta-blockers; CCBs – Calcium channel blockers; ACEIs – Angiotensin converting enzyme; AHT – Antihypertensive; ARBs – Angiotensin receptor blockers; RRP - Recommended retail price; NHS – National Health Service

Table 5: Study variables (continuation)

Variables for prescription characterization		
Variable	**Categories (if applicable)**	**Source**
Drug classification	Single pill/fixed-dose combination	determined using ATC code
Duration of prescription End date of prescription	(in days)	calculated using date of prescription, units per package and defined standard dosing
Variables for dispensing characterization		
Variable	**Categories (if applicable)**	**Source**
Date of dispensing		extracted from SIARS
(Data per drug): ATC code Drug class Brand/Generic name Strenght Number of packages Units per package RRP / reference price Cost for the NHS Cost for patient Drug classification	 ATC code – 5th level Diuretics, BBs, CCBs, ACEIs, ARBs, Other AHT (ATC code – 2nd level) minimum: 1; maximum: 6	extracted from SIARS determined using ATC code
Duration of dispensing End date of dispensing	(in days)	calculated using date of dispensing, units per package and defined standard dosing
Healthcare providing system	PHC sector, Public Hospitals, Private practice	extracted from SIARS

Legend: ATC code - Anatomical Therapeutic Chemical code; SIARS – Information System of the Regional Health Administration; BBs – Beta-blockers; CCBs – Calcium channel blockers; ACEIs – Angiotensin converting enzyme; ARBs – Angiotensin receptor blockers; AHT – Antihypertensive; RRP - Recommended retail price; NHS – National Health Service; PHC – Primary Health Care

Table 5: Study variables (continuation)

Variables for treatment characterization		
Variable	**Categories (if applicable)**	**Source**
Number of AHT drugs prescribed	continuous categorical: 1; 2; 3 or more	calculated
Number of AHT drugs dispensed	continuous categorical: 1; 2; 3 or more	calculated
Initial drug class	Diuretics, diuretics combination, BBs, CCBs, ACEIs, ACEIs combination, ARBs, ARBs combination, Other AHT, two or more drug classes	determined using ATC code
Number of prescribers	continuous categorical: 1; 2; 3 or more	calculated
Variables for adherence characterization		
Variable	**Formula**	**Source**
Rate of primary adherence	number of claims records / number of prescriptions records	calculated after linkage of prescriptions and claims records
Rate of initiation	number of new users / total number of cohort members	calculated after linkage of prescriptions and claims records
Time to initiation	index date – date of index prescription (in days)	calculated after linkage of prescriptions and claims records
Rate of early discontinuation	number of early discontinuers / total number of new users	calculated
Rate of discontinuation	number of discontinuers (non-persistent) / total number of new users	calculated
Time to discontinuation	discontinuation date – index date (in days)	calculated
MPR	see section 5.4.3.	calculated

Legend: AHT – Antihypertensive; BBs – Beta-blockers; CCBs – Calcium channel blockers; ACEIs – Angiotensin converting enzyme; ARBs – Angiotensin receptor blockers; ATC code - Anatomical Therapeutic Chemical code; MPR – Medication Possession Ratio

5.8. DATA ANALYSIS

We've started by pre-processing raw data provided by ARSLVT in *Microsoft Excel* files in order to check for incomplete data, errors or outliers and discrepancies in codes or names. The application of exclusion criteria excluded all patients who didn't comply with criteria set in advance for this study.

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

- Time to initiation;
- Defined standard dosing for each dispensing
- Duration (in days) and end date of each prescription;
- Gap between prescriptions (in days);
- Time to discontinuation;
- MPR per drug (ATC code – 5th level) and per patient.

This was performed using *Microsoft Excel* 2013.

These data allowed the characterization of patients concerning to the study outcomes: initiation, implementation and discontinuation of AHT therapy.

For baseline description, all patients with index diagnoses and index prescription during the first trimester of 2011 were included.

Continuous, e.g., numerical variables were described using standard statistical measures: number of observations, mean, standard deviation, median, minimum and maximum values. Categorical variables were analysed to determine absolute and relative frequencies. When appropriate, to test differences in demographic and other characteristics between groups of patients (i.e. adherent and non-adherent or persistent and non-persistent), several statistical tests were used (as mentioned in section 5.4.).

The statistical analysis was performed using SPSS, version 23, a level of significance of 5% being used in comparative analyses ($p<0.05$).

5.9. DATA PERMIT PROCESS:

This study was approved by the ethics committee of ARSLVT – protocol number 119/CES/INV2013 and by the Ethics Research Committee of NOVA Medical School/Faculty of Medical Sciences – project number 40/2014/CEFCM.

CHAPTER 6: STUDY RESULTS

6.1. PATIENTS' CHARACTERISTICS

During the first trimester of 2011, 29,896 patients were diagnosed with hypertension – ICPC-2 codes k86 and k87 – in the PHC units of Lisbon and Tagus Valley Region. For those patients, prescriptions and claims records for AHT drugs were collected from SIARS and provided by ARSLVT in two separate *Microsoft Excel* files, one with the prescriptions records for the 29,896 patients and the other with the claims records for 28,121 of those patients.

Figure 5 shows the flow chart of the application of the exclusion criteria.

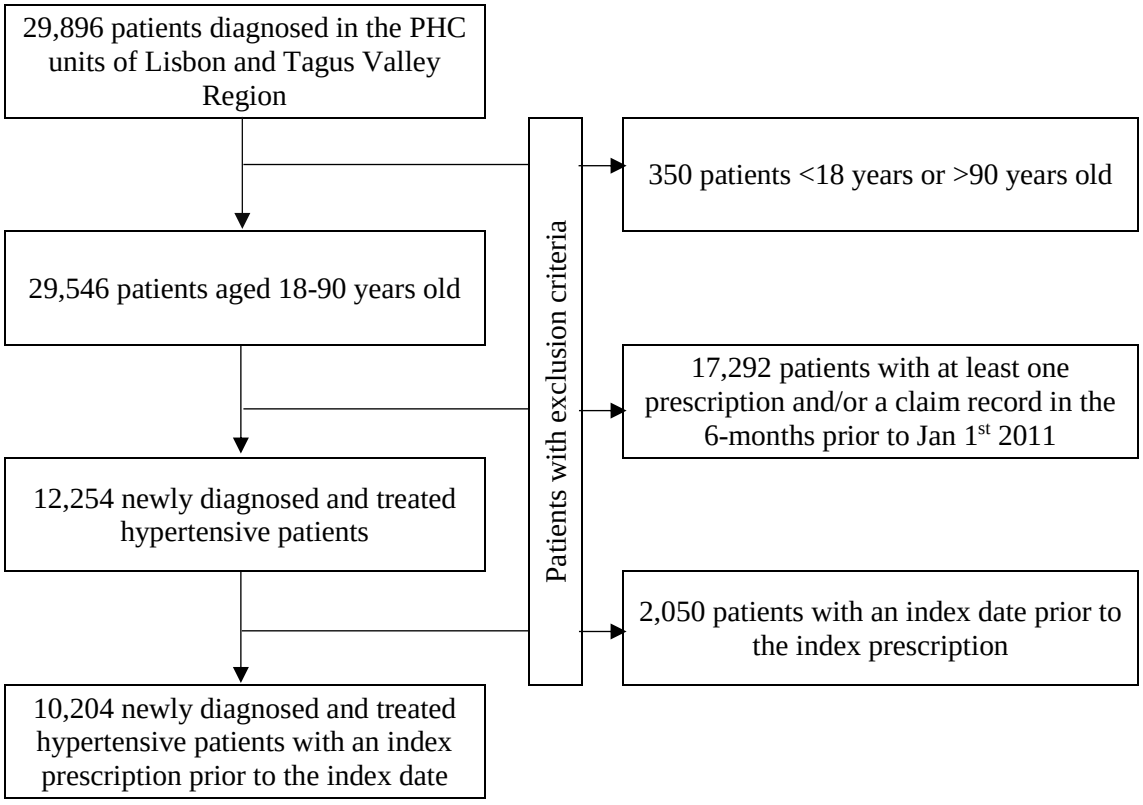

Figure 5. Flow chart of inclusion and exclusion criteria

After excluding all patients who didn't comply with the criteria set in advance in the prescriptions records file, the same was done in the claims records file, i.e. every patient who was excluded from the first file was also excluded from the latter.

After applying the exclusion criteria, prescriptions records file included 68,206 records corresponding to 182,841 packages of AHT drugs for the 10,204 newly diagnosed and treated hypertensive patients and claims records file included 140,154 records for 9,715

patients. Table 6 shows baseline characteristics of patients enrolled in the study, i.e. the cohort members.

Table 6. Baseline characteristics of patients enrolled in the study

Patients' characteristics	men	women	total
	4,645 (45.5%)	5,559 (54.5%)	10,204
Age			
mean (±SD)	60.5±12.8	61.5±13.2	61.0±13.0
18 to 44	482 (10.4%)	548 (9.9%)	1,030 (10.1%)
45 to 64	2,223 (47.2%)	2,487 (44.7%)	4,710 (46.2%)
65 or more	1,940 (41.8%)	2,524 (45.4%)	4,464 (43.7%)
Region (NUTS III)[a]			
Great Lisbon	2,490 (53.7%)	3,230 (58.1%)	5,720 (56.1%)
Setubal Peninsula	885 (19.1%)	925 (16.6%)	1,810 (17.8%)
Middle Tagus	304 (6.6%)	344 (6.2%)	648 (6.4%)
West	524 (11.3%)	526 (9.5%)	1,052 (10.3%)
Leziria West Coast	435 (9.4%)	532 (9.6%)	967 (9.5%)
Buying power			
<100	1,548 (33.3%)	1,698 (30.5%)	3,246 (31.8%)
[100-200[	2,541 (44.9%)	3,124 (55.1%)	5,665 (55.5%)
≥200	556 (12.0%)	737 (13.3%)	1,293 (12.7%)
ICPC-2 code[b]			
k86	3,147 (91.3%)	3,971 (95.0%)	7,118 (93.3%)
k87	301(8.7%)	210 (5.0%)	511(6.7%)

Legend: SD – Standard deviation; NUTS – Nomenclatura das Unidades Territoriais para Fins Estatísticos; ICPC-2 – International Classification for Primary Care, 2nd edition

[a] data missing for 9 patients; [b] data missing for 2,575 patients

The age of the cohort members ranged between 18 and 90 years, with a mean age of 61.0±13.0 years and a median age of 61.0 years. The mean age of men (45.5% of total) was 60.5±12.8 years and of women 61.5±13.2 years. The age difference between gender, although small, was statistically significant ($p<0.001$).

Approximately ¾ (73.9%) of the cohort members were living in the first trimester of 2011 in the Lisbon Metropolitan Area (LMA), which includes the regions of Great Lisbon and

Setubal Peninsula. Although LMA accounts only for about 3.2% of the Portuguese territory, it includes 26.5% of the Portuguese population[164]. Patients from the rural areas and the interior (i.e. Middle Tagus, West and Leziria West Coast regions) were older (61.3±13.0 years) than patients from the LMA (60.3±13.1 years). This age difference between the regions was also statistically significant (p<0.001), reflecting a higher *Ageing Index*[iv] of these areas of residence.

Using the patient's housing parish code, we were also able to determine individual's buying power, extracting that information from the Pordata website (www.pordata.pt). Almost one out of three (31.7%) of the cohort members were living in poorer municipalities, i.e. with a buying power lower than 100. Patients living in municipalities with a higher buying power were older (61.3±13.1 years) than those with a lower buying power (60.4±12.9 years). This age difference was also statistically significant (p=0.001).

The large majority (93.3%) of patients were diagnosed by PHC physicians with ICPC-2 code k86 (hypertension without complications), in spite of differences found considering the gender and the age of the patients; k87 diagnosis code was higher among male and older patients (p<0.001). However, the actual ICPC-2 code was not provided for every patients. In fact, despite our efforts, that specific information was missing for 2,575 (25.2%) patients.

Worth mentioning is that even though our results reflect incidence of hypertension, they are very much consistent with previous findings on the prevalence of hypertension in the Portuguese population, including the PHYSA study[16] and the PAP study[44], where in both studies, the authors found that prevalence of hypertension in Portugal increased with advancing age, and it was higher in men compared with women in groups aged below 64 years, but not beyond that age.

[iv] The ***Ageing Index*** correspond to the number of people aged 65 or more per 100 people under 15 years. A value lower than 100 means that there are fewer elderly people than young people (http://www.pordata.pt/Municipios/%C3%8Dndice+de+envelhecimento-458 (5-08-2015)

6.2. PRESCRIPTIONS AND CLAIMS RECORDS ANALYSIS

6.2.1. Prescriptions records analysis

As mentioned, prescriptions records are referent only to PHC units. For the cohort members, we found that on average, PHC physicians prescribed 3.0±1.0 different AHT drugs (in terms of ATC codes – 5th level[v]) throughout the two-year observation period for each patient (range: 1-10), irrespectively of the new drugs being an addition or a substitution to the initially prescribed ones; for each AHT drug, were prescribed 3.0±2.8 packages, irrespectively of the package size (range: 1-40).

The proportion of patients prescribed with a single AHT drug (ATC code – 5th level) was 48.5%, slightly higher in men (49.1% *vs* 48.1% in women), decreasing with age (59.4% in the 18-44 age group and 42.3% in the 65 or more group). Younger patients were predominantly treated with a single AHT drug (men: 63.1%; women: 56.3%) during the observation period and older patients with two or more drugs, irrespectively of the occurrence of additions and/or substitutions to the initially prescribed ones (men: 56.2% and women: 57.7%) (Figure 6).

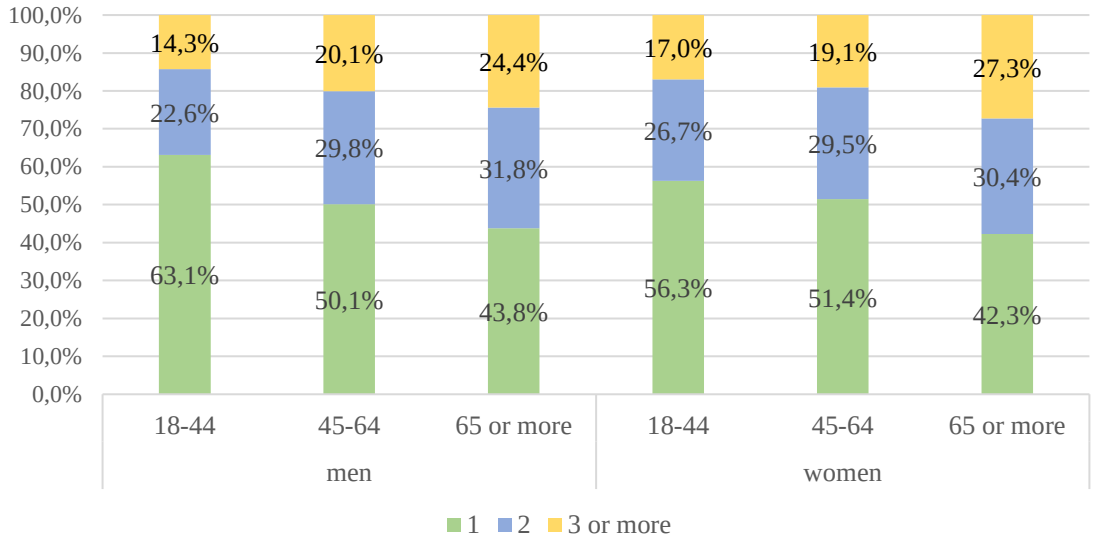

Figure 6. Number of prescribed AHT drugs, by age group and gender

Overall, agents acting on the Renin-angiotensin system (RAS) (ATC code 2nd level C09), in monotherapy or in fixed-dose combinations with other drugs were the most prescribed

[v] In this case, a fixed-dose combination is counted as an individual drug.

AHT drugs throughout the observation period for the cohort members by the PHC physicians. Together, ARBs in fixed-dose combinations (24.4%); ACEIs (13.9%); ACEIs in fixed-dose combinations (13.9%); and ARBs (13.0%) corresponded to approximately two out of three (≈65%) prescribed AHT drugs. Table 7 presents the distribution of the prescribed AHT drugs, by ATC code, 2nd and 3rd levels, throughout the observation period.

Table 7. Prescribed AHT drugs during the observation period, by ATC code

ATC code	**n (%) total** n (%) in drug class
C02 – Antihypertensives:	**1,260 (0.7%)**
C02A – Antiadrenergic agents, centrally acting	1,153 (91.5%)
C02C – Antiadrenergic agents, peripherally acting	107 (8.5%)
C03 – Diuretics:	**21,507 (11.8%)**
C03B – Low-ceiling diuretics, excl. thiazides	14,511 (67.5%)
C03C – High-ceiling diuretics	4,195 (19.5%)
C03D - Potassium-sparing agents	142 (0.7%)
C03E – Diuretics and potassium-sparing agents in combination	2,659 (12.3%)
C07 – Beta blocking agents	**19,771 (10.8%)**
C08 – Calcium channel blockers	**19,213 (10.5%)**
C08C – Selective CCBs with mainly vascular effects	17,248 (89.8%)
C08D - Selective CCBs with direct cardiac effects	1,965 (10.2%)
C09 - Agents acting on the renin-angiotensin system	**121,090 (66.2%)**
C09A – ACE inhibitors, plain	25,437 (21.0%)
C09B - ACE inhibitors, combinations	25,389 (21.0%)
C09C – Angiotensin II antagonists, plain	23,777 (19.6%)
C09D - Angiotensin II antagonists, combinations	44,547 (36.8%)
C09X – Other agents acting on the renin-angiotensin system	1,940 (1.6%)
Total	**182,841**

Legend: ATC code – Anatomical Therapeutic Chemical code; CCBs – Calcium channel blockers; ACE - Angiotensin converting enzyme.

Fixed-dose combinations, i.e. the combination of one diuretic and one ACEI or ARB or the combination of one ACEI or ARB and one CCB, represented 39.7% of all prescribed AHT drugs during the observation period. If fixed-dose combinations were counted

twice, both in the diuretic or CCBs group and in the ACEIs or ARBs groups, diuretics (29.9%), ARBs (27.0%), and ACEIs (20.1%) were the most frequently prescribed AHT drug classes by PHC physicians for hypertension treatment for the cohort members.

Considering the prescription by brand or generic name, we've found that 54.3% of all prescribed AHT drugs throughout the observation period corresponded to brand named drugs (from 44.3% in the diuretics class – ATC code C03 – to 96.9% of all antihypertensives – ATC code C02), while generic drugs accounted for 45.7% of the prescribed drugs (over 50% for diuretics, CCBs, and BBs – 55.7%, 52.3% and 50.8%, respectively (Figure 7).

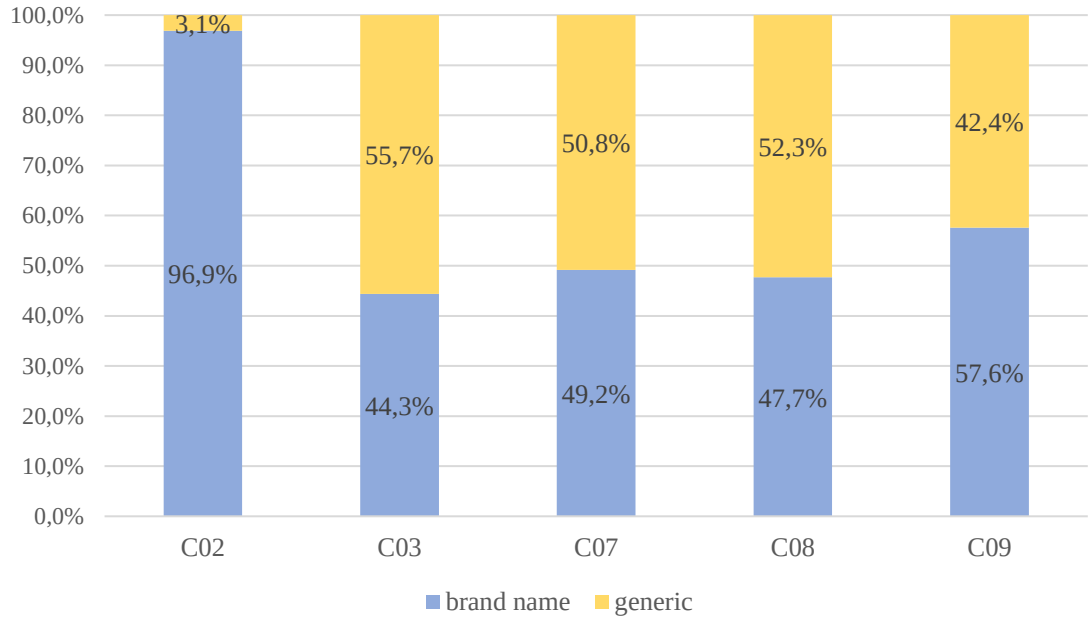

Figure 7. Generic and brand named AHT drugs prescribed during the observation period
Legend: C02 – Antihypertensives; C03 – Diuretics; C07 – Beta blocking agents; C08 - Calcium channel blockers; C09 - Agents acting on the renin-angiotensin system

Looking at the AHT drug classes specifically prescribed per patient during the observation period, diuretics, alone or in combination with an ACEI or an ARB, were prescribed for almost 60% of patients, followed by ARBs (54.0%) and ACEIs (46.4%), irrespectively of the number of records for each drug class. Worth mentioning that in this analysis of prescribed drug classes per patient, if a patient was initially treated with an ARB alone, for example, and later on switched to an ARB in a fixed-dose combination, the drug class was only counted once (Table 8).

Table 8. Proportion of AHT drug classes prescribed per patient, by gender

AHT drug classes	men	women	total
	4,645 (45.5%)	5,559 (54.5%)	10,204
Diuretics	2,657 (57.2%)	3,452 (62.1%)	6,109 (59.9%)
BBs	745 (16.0%)	1,052 (18.9%)	1,797 (17.6%)
CCBs	1,724 (37.1%)	1,843 (33.2%)	3,567 (35.0%)
ACEIs	2,266 (48.8%)	2,467 (44.4%)	4,733 (46.4%)
ARBs	2,503 (53.9%)	3,010 (54.1%)	5,513 (54.0%)
Other AHT	126 (2.7%)	154 (2.8%)	280 (2.7%)

Legend: AHT – Antihypertensive; BBs – Beta-blockers; CCBs – Calcium channel blockers; ACEIs – Angiotensin converting enzyme; ARBs – Angiotensin receptor blockers

The differences found in the proportion of AHT drug classes prescribed per patient between men and women, were statistically significant ($p<0.001$) for all classes, except for ARBs and the 'other' AHT. The proportion of prescribed diuretics, BBs and ARBs was higher in women while the proportion of CCBs and ACEIs was higher in men.

Analysing the proportion of prescribed AHT drugs per patient, accordingly to the age group, we've found that prescription increased with age for diuretics and CCBs, and decreased for BBs. In the other drug classes, prescription increased from the 18-44 age group to the 45-64 age group and diminish to the 65 or more age group. These differences were statistically significant ($p<0.001$) for all drug classes.

Figure 8 shows the proportion of AHT drug classes prescribed per patient during the observation period, according to the age groups.

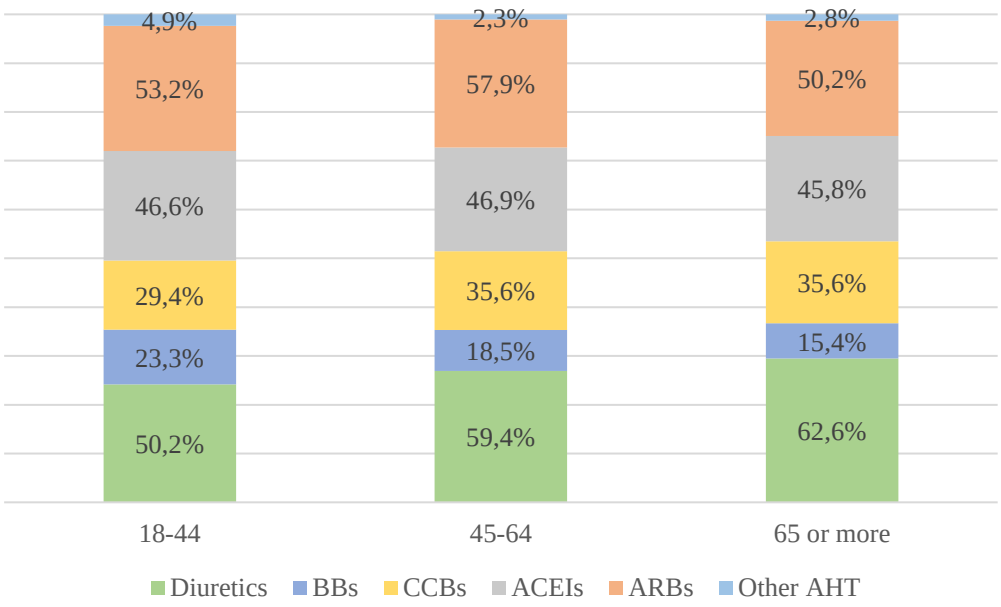

Figure 8. Proportion of AHT drug classes prescribed per patient, by age group

Legend: BBs – Beta-blockers; CCBs – Calcium channel blockers; ACEIs – Angiotensin converting enzyme; ARBs – Angiotensin receptor blockers; AHT – Antihypertensives

6.2.2. Linkage between prescriptions and claims records for determining primary adherence rate

Overall, 107,024 (58.5%) of the 182,841 AHT drugs prescribed by the PHC physicians during the observation period were dispensed in a pharmacy, i.e. originated a claim record.

The rate of primary adherence increased with age ($p<0.001$), and it was higher for men ($p=0.020$).

For patients living in the LMA, primary adherence rates were lower than for the rural areas and the interior ($p<0.001$), although, in terms of patient's buying power, there were no differences (in fact, aggregating buying power ≥100, the proportion was 58.5%, the same for the lowest buying power) ($p=0.788$)

Primary adherence rates were also higher for patients diagnosed with ICPC-2 code k86 ($p=0.001$). All results are shown in Table 9.

Table 9. Rate of primary adherence, by patients' characteristics

Patients' characteristics	Prescribed drugs	Dispensed drugs (%)	*p*-value
Total	182,841	107,024 (58.5%)	
Gender			0.020
male	82,382	48,947 (59.4%)	
female	100,459	58,077 (57.8%)	
Age			<0.001
18 to 44	12,113	6.662 (55.0%)	
45 to 64	76,952	44,239 (57.5%)	
65 or more	93,776	56,123 (59.8%)	
Region (NUTS III)[a]			<0.001
Great Lisbon	106,188	61,745 (58.1%)	
Setubal Peninsula	32,182	18,611 (57.8%)	
Middle Tagus	10,336	6,172 (59.7%)	
West	17,720	10,771 (60.8%)	
Leziria West Coast	16,244	9,629 (59.3%)	
Buying power[a]			0.788
<100	57,619	33,727 (58.5%)	
[100-200[	103,523	60,909 (58.8%)	
≥200	21,528	12,297 (57.1%)	
ICPC-2 code[b]			0.001
k86	134,778	84,059 (62.4%)	
k87	12,609	7,386 (58.6%)	

Legend: NUTS – Nomenclatura das Unidades Territoriais para Fins Estatísticos; ICPC-2 – International Classification for Primary Care, 2nd edition

[a] Data missing for 171 prescriptions records; [b] Data missing for 34,454 prescriptions records

As the literature shows, a good physician-patient relationship improves adherence to medications[23;148-151]. In this primary adherence analysis, we found that the proportion of prescribed drugs that were dispensed was slightly higher when the drug was prescribed by the patient's family doctor (58.9% *vs* 58.1%), although that difference was not statistically significant (p=0.117).

Considering the effect of drug classes on primary adherence rates, ARBs, alone or in fixed-dose combinations with a diuretic or a CCB, ACEIs in fixed-dose combinations and BBs were the drug classes with the highest primary adherence rates, while CCBs and

diuretics, alone or in combination with potassium-sparing agents had the lowest rates (Table 10).

Table 10. Rate of primary adherence, by drug classes

	Prescribed drugs		Dispensed drugs (primary adherence rate)		
	Brands	Generics	Brands	Generics	Total
Drug classes					
Diuretics					
plain	7,510	11,338	4,204 (56.0%)	6,603 (58.2%)	57.3%
combination	2,028	631	1,108 (54.6%)	341 (54.0%)	54.5%
BBs	9,718	10,053	5,803 (59.7%)	5,862 (58.3%)	59.0%
CCBs	9,160	10,053	5,386 (58.8%)	5,376 (53.5%)	56.0%
ACEIs					
plain	6,795	18,642	4,029 (59.3%)	10,684 (57.3%)	57.8%
combination	12,329	13,060	7,150 (58.0%)	7,856 (60.2%)	59.1%
ARBs					
plain	13,843	9,934	8,220 (59.4%)	5,823 (58.6%)	59.1%
combination	34,812	9,735	20,583 (59.1%)	6,216 (63.9%)	60.2%
Other AHT	3,161	39	1,757 (55.6%)	23 (59.0%)	55.6%

Legend: BBs – Beta-blockers; CCBs – Calcium channel blockers; ACEIs – Angiotensin converting enzyme; ARBs – Angiotensin receptor blockers; AHT – Antihypertensive

Both ARBs and ACEIs in fixed-dose combinations had higher primary adherence rates compared to their 'plain' formulations, in both cases with higher rates for generic drugs. Overall, we found no differences in the primary adherence rates of prescribed generic or brand name drugs ($p=0.710$). However, when we analysed each drug class in separate, we found statistically significant differences for almost every AHT drug classes ($p<0.001$), except for diuretics in fixed-dose combinations, and the 'other' AHT.

Analysing the effect of the out-of-pocket cost for the patients of the prescribed drugs in the rate of primary adherence, we've found that its increase was associated with a decrease in the primary adherence rate ($p<0.001$), more relevant for diuretics and BBs and less relevant for drugs acting on the RAS and CCBs (Figure 9).

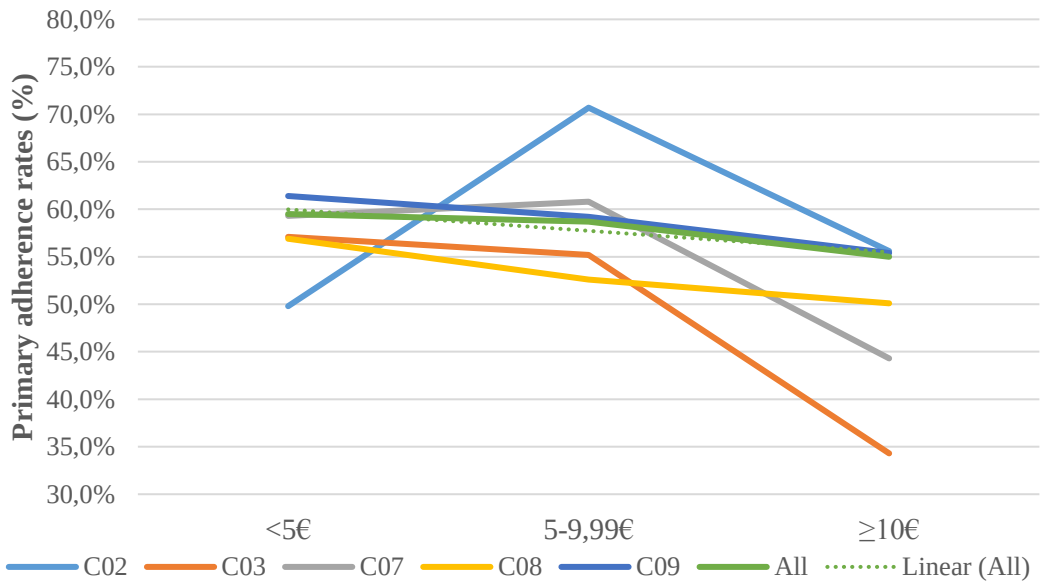

Figure 9. Effect of out-of-pocket costs in primary adherence rates, by drug classes

Legend: C02 – Antihypertensives; C03 – Diuretics; C07 – Beta-blockers; C08 – Calcium channel blockers; C09 – Agents acting on the renin-angiotensin system

6.2.3. Claims records analysis

Analysing the claims records of AHT drugs dispensed for the cohort members, we found that on average, 1.9±2.1 AHT drugs (in terms of ATC codes – 5th level) were dispensed per patient during the two-year observation period (range: 1-12), irrespectively of the new drugs being an addition or a substitution to the initially prescribed ones; for each AHT drug, 3.9±2.8 packages (range: 1-25) were dispensed, irrespectively of the package size.

The large majority (76.4%) of dispensed AHT drugs were originated from PHC physicians. Table 11 presents the distribution of all claims records for dispensed AHT drugs during the observation period for the cohort members, taking in consideration the healthcare providing system.

Table 11. Distribution of claims records, by healthcare providing system

ATC Code	PHC sector	Public Hospitals	Private practice	**n (%) total** n (%) in group
Total	107,024	23,023	10,107	**140,154**
Diuretics	**12,256 (11.5%)**	**3,614 (15.7%)**	**1,294 (12.8%)**	**17,164 (12.3%)**
plain	10,807	3,454	1,106	15,367 (89.5%)
combination	1,449	160	188	1,797 (10.5%)
BBs	**11,665 (10.9%)**	**3,522 (15.3%)**	**1,304 (12.9%)**	**16,491 (11.8%)**
CCBs	**10,762 (10.1%)**	**3,131 (13.6%)**	**1,122 (11.1%)**	**15,015 (10.7%)**
ACEIs	**29,719 (27.8%)**	**6,285 (27.3%)**	**2,102 (20.8%)**	**38,106 (27.2%)**
plain	14,713	4,006	1,020	19,739 (51.8%)
combination	15,006	2,279	1,082	18,367 (48.2%)
ARBs	**40,842 (38.2%)**	**5,985 (26.0%)**	**3,972 (39.3%)**	**50,799 (36.3%)**
plain	14,043	2,352	1,150	17,545 (34.5%)
combination	26,799	3,633	2,826	33,258 (65.5%)
Other AHT	**1,780 (1.7%)**	**506 (2.2%)**	**313 (3.1%)**	**2,599 (1.8%)**

Legend: ATC – Anatomical Therapeutic Chemical; PHC – Primary Healthcare; BBs – Beta-blockers; CCBs – Calcium channel blockers; ACEIs – Angiotensin converting enzyme; ARBs – Angiotensin receptor blockers; AHT – Antihypertensive.

Together, ARBs in fixed-dose combinations (23.7%); ACEIs (14.1%); ACEIs in fixed-dose combinations (13.1%); and ARBs (12.5%) accounted for 63.4% of all dispensed AHT drugs.

Still, the proportion of claims by drug classes was not the same when considering the healthcare providing system where the prescription was originated from. For ACEIs and ARBs, it was higher for prescriptions originated from the PHC sector, compared to public hospitals, while for all the other drug classes, it was higher for public hospitals or the private sector. These differences were statistically significant ($p<0.001$), implying different prescription patterns for hypertension treatment throughout the healthcare system.

During the observation period, patients purchased drugs prescribed by 1.7±0.8 prescribers (range: 1-9).

Since our data indicated a rather low primary adherence rate for AHT drugs prescribed by the PHC physicians, we repeated the analysis that we've conducted for prescriptions records, regarding the proportion of patients being treated with a single AHT drug or a combination of two or more drugs, now using the claims records, more close to the actual treatment patterns.

The proportion of patients being treated with a single AHT drug was 47.6%, higher in men (48.7% *vs* 46.6% in women), decreasing with age (60.2% in the 18-44 age group and 41.7% in the 65 or more group). Younger patients were predominately treated with a single AHT drug (men: 62.7%; women: 58.1%) during the observation period and older patients with two or more drugs, irrespectively of the new drugs being an addition or a switch to the initially prescribed ones (men: 57.1% and women: 59.1%) (Figure 10).

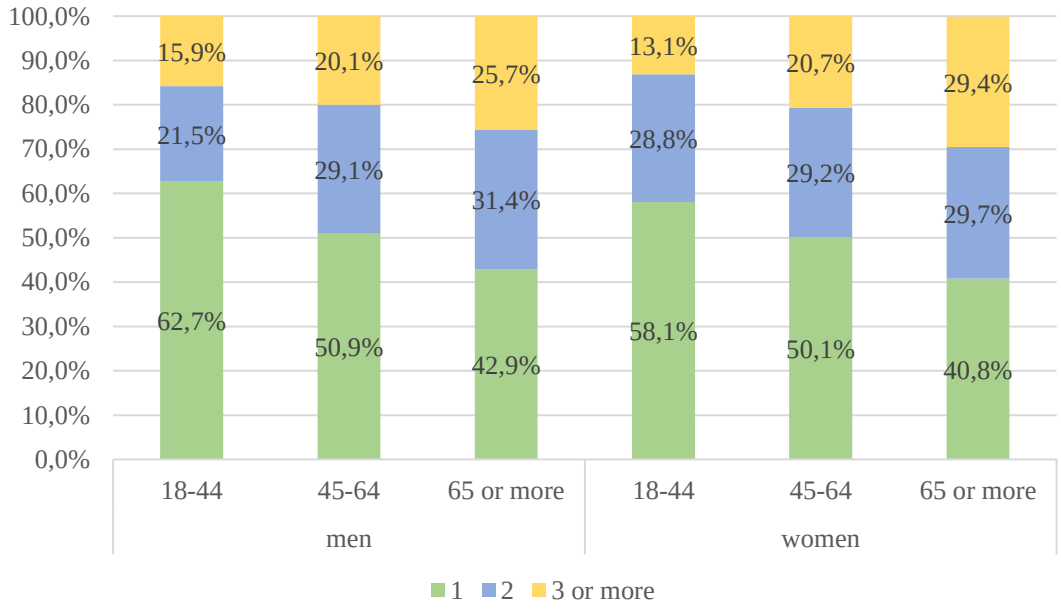

Figure 10. Number of AHT drugs dispensed per patient, by age group and gender

6.3. ADHERENCE MEASURES

6.3.1. Initiation of antihypertensive therapy

Of the 10,204 newly diagnosed and treated hypertensive patients, 8,856 (86.8%) initiated hypertension treatment within six months after index prescription and therefore were

classified as 'new users' of AHT therapy. The remaining 1,348 (13.2%) patients were classified as 'non-users'. Characteristics of both groups are shown in Table 12.

Table 12. Initiation of AHT therapy, by patients' characteristics

Patients' characteristics	New users	Non-users	*p*-value
Total	8,856 (86.8%)	1,348 (13.2%)	
Gender			p = 0.226
male	4,052 (87.2%)	593 (12.8%)	
female	4,804 (86.4%)	755 (13.6%)	
Age			p <0.001
18 to 44	885 (85.9%)	145 (14.1%)	
45 to 64	4,027 (85.5%)	683 (14.5%)	
65 or more	3,944 (88.4%)	520 (11.6%)	
Region (NUTS III)[a]			p = 0.204
Great Lisbon	4,947 (86.5%)	773 (13.5%)	
Setubal Peninsula	1,585 (87.6%)	225 (12.4%)	
Middle Tagus	561 (86.6%)	87 (13.4%)	
West	930 (88.6%)	120 (11.4%)	
Leziria West Coast	826 (85.4%)	141 (14.6%)	
Buying power			p = 0.007
<100	2,843 (87.6%)	403 (12.4%)	
[100-200[	4,926 (87.0%)	739 (13.0%)	
≥200	1,087 (84.1%)	206 (15.9%)	

Legend: NUTS – Nomenclatura das Unidades Territoriais para Fins Estatísticos;

[a] data missing for 9 patients

Male and older patients (65 years or older) shown higher initiation rates, although there was no statistically significant difference between gender (p=0.226).

In our study, we've also found that there was also no difference in initiation rates between regions although patients living in municipalities with a lower buying power had a higher initiation rate (p=0.007).

Due to missing data of the actual ICPC-2 code for every patients, we weren't able to analyse the association between the diagnosis code and the initiation of AHT therapy.

Like for primary adherence rates, we found no differences in the proportion of patients who initiated AHT therapy after being diagnosed and received a prescription by their family doctor or by another PHC physician (84.7% *vs* 85.2%; p=0.622).

Looking at the initially prescribed drug classes, combination therapy of two or more AHT drugs – either as a fixed-dose combination or as two or more drugs taken separately - was the first choice for 5,427 (52.2%) of the cohort members (Table 13).

Table 13. Initiation of AHT therapy, by drug classes

Drug classes	New users	Non-users	Total
Total	8,856 (86.8%)	1,348 (13.2%)	**n (%) total**
Single pill / monotherapy			
Diuretics	658 (85.5%)	112 (14.5%)	770 (7.5%)
BBs	448 (84.1%)	85 (15.9%)	533 (5.2%)
CCBs	340 (84.6%)	62 (15.4%)	402 (3.9%)
ACEIs	1,392 (86.0%)	227 (14.0%)	1,619 (15.9%)
ARBs	1,231 (85.9%)	202 (14.1%)	1,433 (14.0%)
Other AHT	92 (84.4%)	17 (15.6%)	109 (1.1%)
Single pill / fixed combination			
ACEI – diuretic/CCB	1,196 (87.2%)	176 (12.8%)	1,372 (13.4%)
ARB – diuretic/CCB	1,923 (85.9%)	316 (14.1%)	2,239 (21.9%)
Diuretics	89 (84.8%)	16 (15.2%)	105 (1.0%)
Combination therapy			
2 or more ATC codes	1,486 (91.6%)	136 (8.4%)	1,622 (15.9%)

Legend: BBs – Beta-blockers; CCBs – Calcium channel blockers; ACEIs – Angiotensin converting enzyme; ARBs – Angiotensin receptor blockers; AHT – Antihypertensive; ATC code - Anatomical Therapeutic Chemical code

Restricting our analysis to patients who initially received a prescription for a single AHT drug (ATC code – 5th level), those who initially received a prescription for an ACEI and/or an ARB, alone or in a fixed-dose combination with a diuretic or a CCB (single pill) had higher initiation rates compared to the other AHT drug classes; initiation rates were lower for BBs and CCBs.

Worth mentioning, is that for the 1,486 patients who initiated hypertension treatment after receiving a prescription of two or more AHT drugs (ATC code – 5th level), 291 (19.6%) actually initiated treatment with only a single AHT drug.

Considering the initially prescribed AHT drugs for hypertension treatment of the cohort members, including double-counting of fixed-dose combinations, diuretics (45.3%), ARBs (44.3%), and ACEIs (36.8%) were the most frequently first prescribed AHT drugs.

An important factor in the decision to initiate hypertension treatment is the out-of-pocket cost for the patient. Our results show that when the cost of the initially prescribed drugs increased, initiation rates decreased. Patients with co-payments under 5€ were more likely to initiate treatment than patients who had to pay over 10€ for the prescribed therapy (88.2% *vs* 83.6%, p <0.001) (Figure 11). Even excluding of patients who were initially treated with two or more AHT drugs (therefore with an expected higher cost), the effect of out-of-pocket cost remained: increased costs reduces initiation rates (p <0.001).

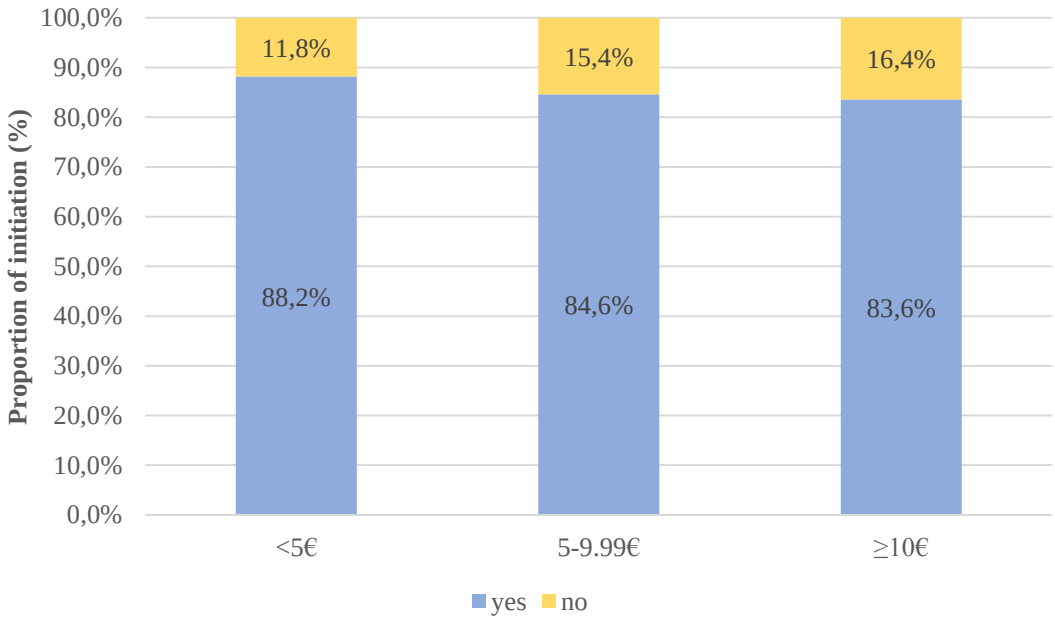

Figure 11. Initiation of AHT therapy, by out-of-pocket cost

To consider the effect of generic or brand name prescribing in the decision to initiate AHT therapy, we've restricted our analysis for data from patients initially prescribed with a single drug, ATC code – 5th level. We found no differences in the proportion of patients who initiated treatment (generic drugs: 86.1% *vs* brand name drugs: 85.6%; p=0.497).

6.3.1.1. Time to initiation

For the new users of AHT therapy, the index date occurred 26.4±27.8 days after index prescription (median=20.0 days), with differences between men and women: women took longer time to initiate therapy (27.0±28.2 days *vs* 25.8±27.3 days for men) and the gender difference increased over time (p=0.024; Figure 12).

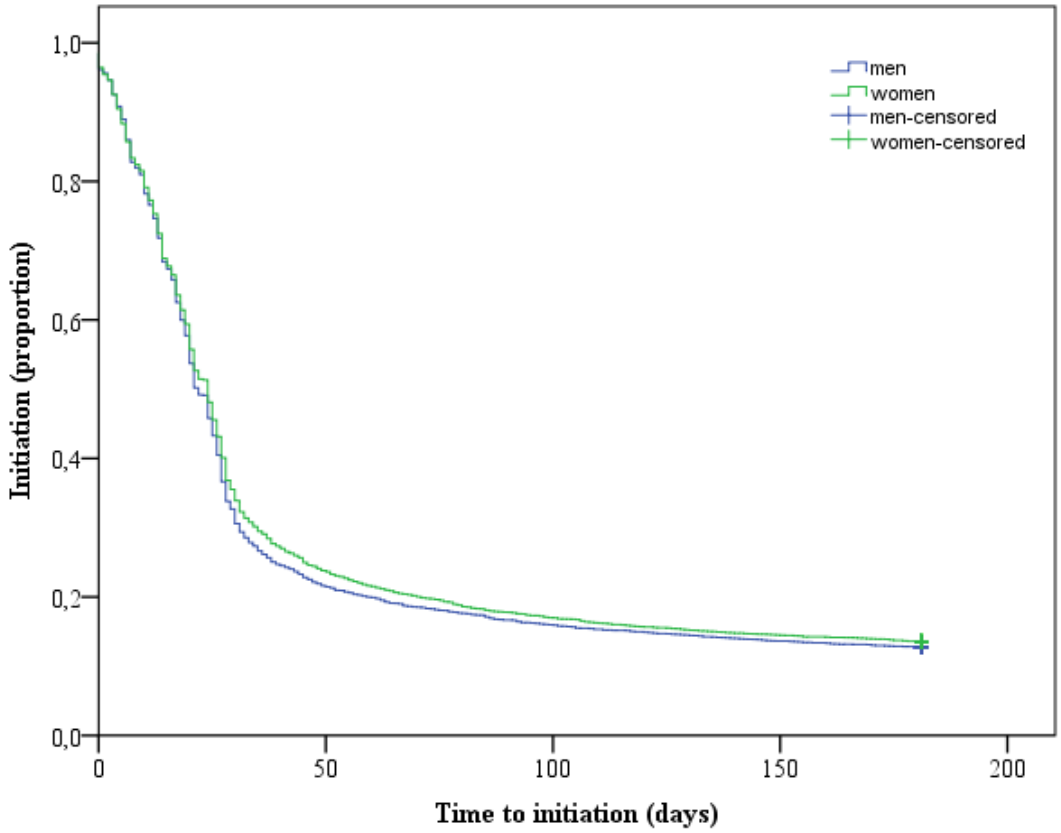

Figure 12. Kaplan-Meier curve of initiation of AHT therapy, by gender

Patients diagnosed with hypertension and treated with at least one AHT drug in the PHC units of Lisbon and Tagus Valley Region (n=10,204) during the 1st trimester of 2011. Crude estimates.

In spite of the highest proportion of older patients (65 or more years) initiating AHT therapy within 6-month after index prescription, time to initiation was lower for younger patients and higher for older patients – 45.4 days for the age group 18-44 and 45.5 for the age group 65 or more (Figure 13). The differences between age groups were also significant (p=0.030).

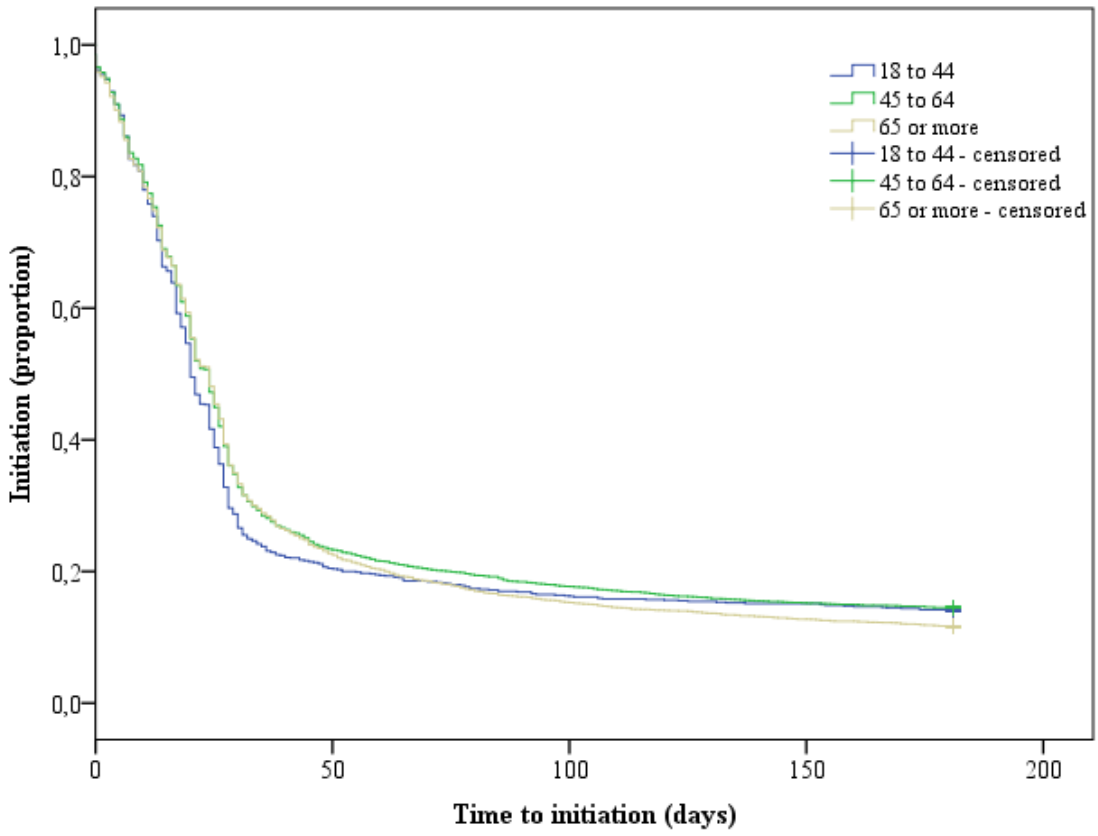

Figure 13. Kaplan-Meier curve of initiation of AHT therapy, by age group

Patients diagnosed with hypertension and treated with at least one AHT drug in the PHC units of Lisbon and Tagus Valley Region (n=10,204) during the 1st trimester of 2011. Crude estimates.

After adjustment for all the potential predictors of time to initiation, the multivariate Cox regression analysis demonstrated gender, age, and initially prescribed drugs (in number and the drug classes) to be important factors associated with timely initiation of AHT therapy. On the other hand, out-of-pocket cost, severity of hypertension (in terms of ICPC-2 code) and patient's buying power had no significant association to initiation after adjustments for all potential predictors (Table 14).

The HR for initiation was 6% higher for women (CI: 1.01-1.12), 22% higher for patients in the 45-64 age group (CI: 1.17-1.34), 44% higher for patients initially prescribed with two or more AHT drugs (ATC code – 5th level) (CI: 1.09-1.89) and was 36% lower for BBs, compared to diuretics (CI: 0.44-0.93).

Table 14. Factors associated with initiation of AHT therapy

	Crude HR[a]	*p*-value	Adjusted HR[a,b]	*p*-value
Gender		0.017		0.028
Men	1 (ref)		1 (ref)	
Women	0.95 (0.91-0.99)	0.017	1.06 (1.01-1.12)	0.028
Age		<0.001		<0.001
18 to 44	1 (ref)		1 (ref)	
45 to 64	0.87 (0.81-0.94)	<0.001	1.22 (1.17-1.34)	<0.001
65 or more	0.82 (0.76-0.88)	<0.001	1.04 (0.98-1.10)	0.204
ICPC-2 code		0.056		0.801
k86	1 (ref)		1 (ref)	
k87	0.92 (0.84-1.00)	0.052	0.99 (0.88-1.10)	0.801
Number of Drugs		<0.001		0.009
one	1 (ref)		1 (ref)	
two or more	0.87 (0.82-0.92)	<0.001	1.44 (1.09-1.89)	0.009
Buying Power		0.011		0.157
<100	1 (ref)		1 (ref)	
100-200	0.93 (0.89-0.97)	0.004	1.08 (0.99-1.18)	0.088
>=200	0.93 (0.87-1.00)	0.051	1.03 (0.95-1.12)	0.456
Drug Class		<.001		0.002
Diuretics	1 (ref)		1 (ref)	
Diuretics Comb	0.74 (0.60-0.93)	0.009	1.01 (0.76-1.34)	0.943
BBs	0.81 (0.72-0.91)	<0.001	0.64 (0.44-0.93)	0.020
CCBs	0.79 (0.69-0.90)	<0.001	0.79 (0.60-1.05)	0.104
ACEIs	0.82 (0.74-0.89)	<0.001	0.80 (0.60-1.07)	0.129
ACEIs comb	0.86 (0.78-0.95)	0.002	0.85 (0.64-1.11)	0.224
ARBs	0.78 (0.71-0.86)	<0.001	0.92 (0.70-1.21)	0.564
ARBs comb	0.81 (0.74-0.88)	<0.001	0.83 (0.63-1.09)	0.178
Other AHT	0.92 (0.74-1.15)	0.475	0.87 (0.66-1.14)	0.306
Two or more	0.71 (0.65-0.79)	<0.001	0.96 (0.70-1.32)	0.813
Out-of-pocket cost		0.827		0.842
<5€	1 (ref)		1 (ref)	
5-9,99€	1.00 (0.95-1.06)	0.970	1.02 (0.95-1.10)	0.607
≥10€	1.02 (0.96-1.08)	0.541	0.93 (0.94-1.12)	0.583

Legend: HR – Hazard ratio

a) calculated with 95% CI; b) Cox regression model including all covariates studied.

Finally, as mentioned in section 2.2, non-adherence to medications can manifest itself in different ways, one of them being 'late initiation'[29]. In this cohort, 855 (8.4%) of non-users actually initiate AHT therapy although it happened with a considerable delay (time to initiation for this patients: 507.2±182.6 days). In fact, during the entire observation period, only 493 (4.8%) of the newly diagnosed patients fail to acquire any prescribed AHT drugs.

6.3.2. Implementation of antihypertensive therapy

Among the new users of AHT therapy, only 456 (5.1%) patients were classified as having a high level of implementation, i.e. MPR≥80% during the two-year observation period. For the remaining patients, 3,866 (43.7%), and 4,534 (51.2%) were classified as having a low or intermediate level of implementation, respectively.

The proportion of men with a high level of implementation was slightly higher (5.4% in men *vs* 4.9% in women), although that difference was not statistically significant (p=0.273).

High adherent patients were predominantly older patients (6.4% of men and 6.6% of women). The differences between age groups in the implementation of AHT therapy during the two-year observation period were statistically significant (p<0.001).

Figure 14 shows the distribution of patients in three levels of implementation of AHT therapy, accordingly to gender and age group.

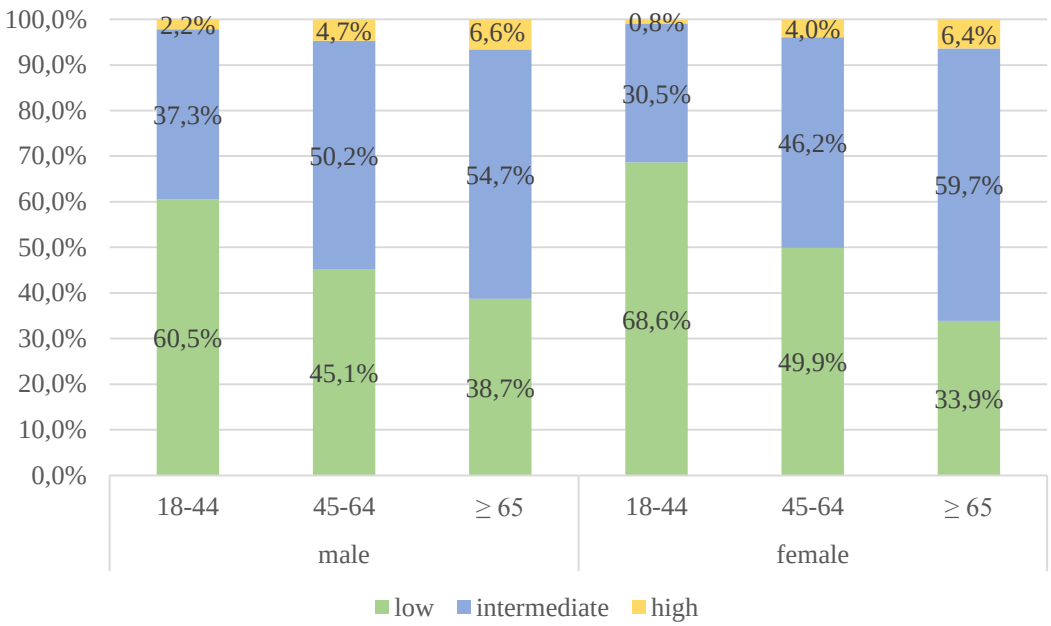

Figure 14. Implementation of AHT therapy, by age group and gender

On average, patients had in their possession, AHT drugs for 43.6±23.1% (in days) of the two-year observation period (median 44.0%). Men had in their possession, AHT drugs for more days than women (43.8±23.5% *vs* 43.4±22.8%). However, the MPR difference between the gender was not statistically significant (p=0.395).

Dichotomizing patients between good implementation (MPR≥80%, adherent patients) and poor implementation (MPR <80%, non-adherent patients), we've found that older patients (65 years or more) had a 3.9 higher implementation rate of AHT therapy than younger patients (18-44 years), being that difference statistically significant (p<0.001).

Although not statistically significant, patients living in poorer municipalities had higher implementation rates (p=0.052).

We found no differences in the implementation of AHT therapy, considering the region where the patient was from (p=0.331) and the diagnosis code of hypertension (p=0.914).

Table 15 shows the differences between both groups.

Table 15. Implementation of AHT therapy, by patients' characteristics

Patients' characteristics	Adherent	Non-adherent	*p*-value
Total	456 (5.1%)	8,400 (94.9%)	
Gender			p = 0.273
male	220 (5.4%)	3,832 (94.6%)	
female	236 (4.9%)	4,568 (95.1%)	
Age			
18 to 44	15 (1.7%)	870 (98.3%)	
45 to 64	181 (4.5%)	3,846 (95.5%)	p <0.001
65 or more	260 (6.6%)	3,684 (93.4%)	
Region (NUTS III)[a]			p = 0.331
Great Lisbon	269 (5.4%)	4,678 (94.6%)	
Setubal Peninsula	74 (4.7%)	1,511 (95.3%)	
Middle Tagus	30 (5.3%)	531 (94.7%)	
West	51 (5.5%)	879 (94.5%)	
Leziria West Coast	32 (3.9%)	794 (96.1%)	
Buying power			p = 0.052
<100	142 (5.0%)	2,701 (95.0%)	
[100-200[	273 (5.5%)	4,653 (94.5%)	
≥200	41 (3.8%)	1,046 (96.2%)	
ICPC-2 code[b]			p = 0.914
k86	382 (5.4%)	6,735 (94.6%)	
k87	28 (5.5%)	483 (94.5%)	

Legend: NUTS – Nomenclatura das Unidades Territoriais para Fins Estatísticos; ICPC-2 – International Classification for Primary Care, 2nd

[a] Data missing for 7 patients; [b] Data missing for 1,228 patients

In terms of drug classes, implementation rates (in terms of MPR) ranged from 42.3% for diuretics and potassium-sparing agents in combination to 48.9% for fixed-dose combinations of an ARB with a diuretics or a CCB. Like we've found for primary adherence rates, ARBs and ACEIs in fixed-dose combinations had higher adherence rates compared to their 'plain' formulations (Figure 15).

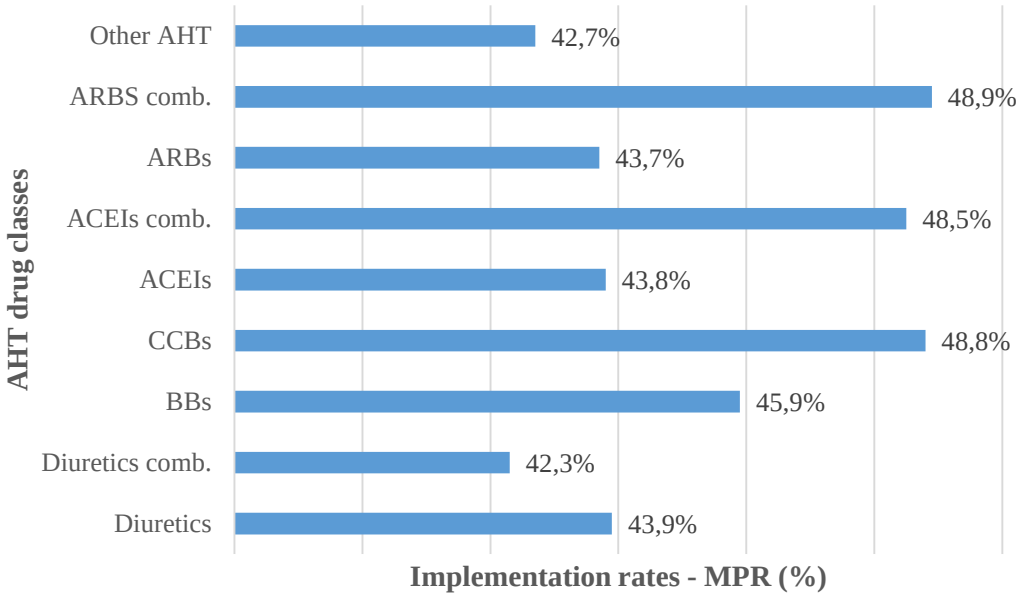

Figure 15. Implementation of AHT therapy, by drug classes

For patients who were treated with a single AHT drug (ATC code – 5th level[vi]), 205 (4.9%) were classified as having a high level of implementation, being that proportion of 5.9% (153 patients) and 4.8% (98 patients) for patients treated throughout the observation period with two or three or more AHT drugs, respectively. However, these differences were not statistically significant (p=0.128).

The number of prescribers involved in hypertension treatment of the cohort members was associated with high levels of implementation of AHT therapy: 7.6% of high adherent patients who received prescriptions from three of more physicians during the observation period *vs* 3.9% who were followed by a single physician (p<0.001).

The logistic regression analysis confirmed age, number of drugs dispensed during the observation period, number of prescribers and patient's buying power to increase the risk of poor implementation of AHT therapy. Gender, ICPC-2 code and initial drug classes, had no significant association to low adherence after adjustments for all potential predictors (Table 16).

[vi] In case of substitution of the initially prescribed drug (in which the patient during the observation period was actually consuming just one drug at the time) we've counted both drugs, in terms of ATC code – 5th level, i.e. the patient was treated with two AHT drugs.

Table 16. Factors associated with poor implementation of AHT therapy

	Crude OR[a]	*p*-value	Adjusted OR[a,b]	*p*-value
Gender		0.273		0.157
Men	1 (ref)		1 (ref)	
Women	1.11 (0.92-1.34)	0.273	1.15 (0.95-1.39)	0.280
Age, years		<0.001		<0.001
18 to 44	1 (ref)		1 (ref)	
45 to 64	0.37 (0.22-0.62)	<0.001	0.38 (0.22-0.65)	<0.001
65 or more	0.24 (0.14-0.41)	<0.001	0.25 (0.15-0.43)	<0.001
Number of Drugs		0.129		0.010
one	1 (ref)		1 (ref)	
two	0.82 (0.66-1.01)	0.067	0.96 (0.77-1.20)	0.717
three or more	1.02 (0.79-1.30)	0.897	1.42 (1.09-1.85)	0.009
Prescribers		<0.001		<0.001
one	1 (ref)		1 (ref)	
two	0.70 (0.56-0.88)	0.002	0.70 (0.55-0.88)	0.002
three or more	0.50 (0.40-0.62)	<0.001	0.48 (0.38-0.61)	<0.001
Buying Power		0.053		0.037
<100	1 (ref)		1 (ref)	
100-200	0.90 (0.73-1.10)	0.720	0.92 (0.74-1.13)	0.413
≥200	1.34 (0.94-1.91)	0.140	1.60 (1.42-0.99)	0.054

Legend: OR – Odds ratio.

[a] Calculated with 95% CI; [b] Logistic regression model, including all covariates studied

After adjustment, the number of dispensed drugs during the observation period increased by 42% (CI:1.09-1.85) the risk of poor implementation of AHT therapy, i.e. non-adherence. Although not statistically significant, data from the logistic regression model shows that higher buying power increases the risk of non-adherence (p=0.054).

6.3.3. Discontinuation of antihypertensive therapy

6.3.3.1. Early discontinuation of antihypertensive therapy

Among the 8,856 new users of AHT therapy, 303 (7.5%) men and 335 (7.0%) women completely discontinued their treatment after being dispensed only one prescription, i.e.

were classified as early discontinuers. Table 17 shows the differences between early discontinuers (non-persistent) and ongoing (persistent) users.

Table 17. Early discontinuation of AHT therapy, by patients' characteristics

Patients' characteristics	Persistent	Non-persistent	*p*-value
Total	8,218 (92.8%)	638 (7.2%)	
Gender			
male	3,749 (92.5%)	303 (7.5%)	p = 0.360
female	4,469 (93.0%)	335 (7.0%)	
Age			
18 to 44	711 (80.3%)	174 (19.7%)	
45 to 64	3,722 (92.4%)	305 (7.6%)	p <0.001
65 or more	3,785 (96.0%)	159 (4.0%)	
Region (NUTS III)[a]			p = 0.012
Great Lisbon	4,609 (93.2%)	338 (6.8%)	
Setubal Peninsula	1,456 (91.9%)	129 (8.1%)	
Middle Tagus	503 (89.7%)	58 (10.3%)	
West	869 (93.4%)	61 (6.6%)	
Leziria West Coast	774 (93.7%)	52 (6.3%)	
Buying power			p = 0.439
<100	2,624 (92.3%)	219 (7.7%)	
[100-200[	4,585 (93.1%)	341 (6.9%)	
≥200	1,009 (92.8%)	78 (7.2%)	
ICPC-2 code[b]			p = 0.003
k86	6,603 (92.8%)	514 (7.2%)	
k87	492 (96.3%)	19 (3.7%)	

Legend: NUTS – Nomenclatura das Unidades Territoriais para Fins Estatísticos; ICPC-2 – International Classification for Primary Care, 2nd

[a] Data missing for 7 patients; [b] Data missing for 1,228 patients

Younger patients were more likely to early discontinue their treatment (p<0.001). In fact, almost one out of five patients under 45 years interrupted their hypertension treatment after the first dispensing.

Complications associated to hypertension seemed to have a positive impact on the decision to continue treatment: 96.3% of patients diagnosed with ICPC-2 code k87

demonstrate an initial engagement with their prescribed treatment, compared to 92.8% of patients diagnosed with ICPC-2 code k86 (p=0.003).

Early discontinuation rates were lower in patients living in the West and Leziria West Coast regions and higher in patients living in the Middle Tagus and Setubal Peninsula regions. These differences were statistically significant (p=0.012). The higher early discontinuation rate in patients living in municipalities with a higher buying power was not statistically significant.

Again, we found no differences in the proportion of patients who early discontinued their hypertension treatment after being diagnosed and receiving a prescription by their family doctor or by another PHC physician (7.6% *vs* 8.5%; p=0.298).

An important aspect to consider in this analysis is that together, 'non-users' of AHT therapy (i.e. late-initiation or absolute non-initiation) and the early discontinuers, account for almost one out of five (19.5%) of the cohort members (n=10,204).

For patients who initiated hypertension treatment with a single AHT drug (in terms of ATC code – 5th level), 1,158 (93.1%) and 1,888 (92.4%) who received a combination of an ACEI or an ARB, respectively, with a diuretic or a CCB were initially engaged with their prescribed treatment.

Higher discontinuation rates were found for patients who initiated AHT therapy with a BB or a diuretic, since 405 (89.2%) and 598 (90.3%) patients were initially engaged with their prescribed treatment.

Patients initiating AHT therapy with a fixed-dose combination were more likely to implement it (at least one more refill) compared to the individual drugs on monotherapy (Table 18).

Table 18. Early discontinuation of AHT therapy, by drug classes

Drug classes	Persistent	Non-persistent	*p*-value
Total	8,218 (92.8%)	638 (7.2%)	
Single pill / monotherapy			p<0.001
Diuretics	598 (90.3%)	64 (9.7%)	
BBs	405 (89.2%)	49 (10.8%)	
CCBs	318 (92.2%)	27 (7.8%)	
ACEIs	1,307 (91.0%)	130 (9.0%)	
ARBs	1,177 (91.6%)	108 (8.4%)	
Other AHT	88 (88.0%)	12 (12.0%)	
Single pill / fixed combination			
ACEI – diuretic/CCB	1,158 (93.1%)	86 (6.9%)	
ARB – diuretic/CCB	1,888 (92.4%)	155 (7.6%)	
Diuretics	84 (92.3%)	7 (7.7%)	
Combination therapy			
2 or more ATC codes	1,195 (100.0%)	0	

Legend: BBs – Beta-blockers; CCBs – Calcium channel blockers; ACEIs – Angiotensin converting enzyme; ARBs – Angiotensin receptor blockers; AHT – Antihypertensive; ATC code – Anatomical Therapeutic Chemical code

As for the decision to initiate treatment (previous to adjustment to other factors), higher out-of-pocket costs contributed to the decision to early discontinue it (12.5% ≥ 10€ compared to 5.7% <5€; p <0.001) (Figure 16). Even excluding patients who were initially treated with two or more AHT drugs (therefore with an expected higher cost), the effect of out-of-pocket cost remained: increased costs reduces initiation rates (p <0.001).

To consider the effect of generic or brand name dispensing in the decision of initial engagement to AHT therapy, we've restricted our analysis for data from patients who initiated treatment with a single drug, ATC code – 5th level. Again, we found no differences in the proportion of patients who early discontinued treatment (generic drugs: 8.7% *vs* brand name drugs: 8.4%; p=0.569).

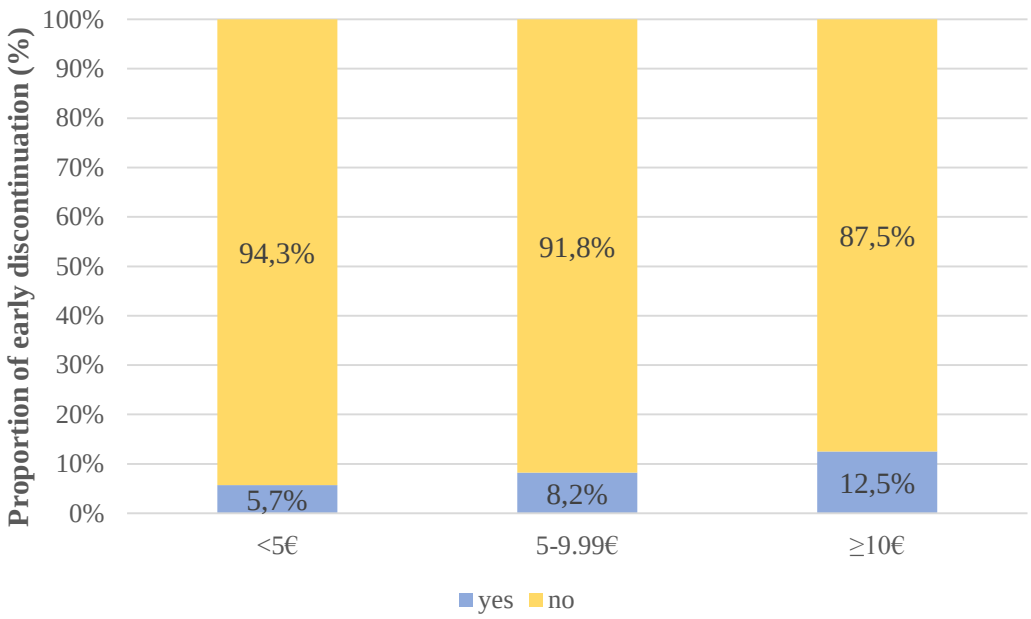

Figure 16. Early discontinuation of AHT therapy, by out-of-pocket cost

6.3.3.2. Two-year persistence to antihypertensive therapy

Among the 8,856 new users of AHT therapy, 21.6% of men and 23.1% of women did not experience any episode of therapy discontinuation (i.e. grace period longer than 90 days) during the first year of hypertension treatment. During the second year, the proportion of continuous/persistent users of AHT therapy dropped dramatically to 5.8% in men and 6.3% in women. The differences between men and women regarding persistence were statistically significant (p=0.037). Women had a higher persistence and the gender difference increased over time (Figure 17).

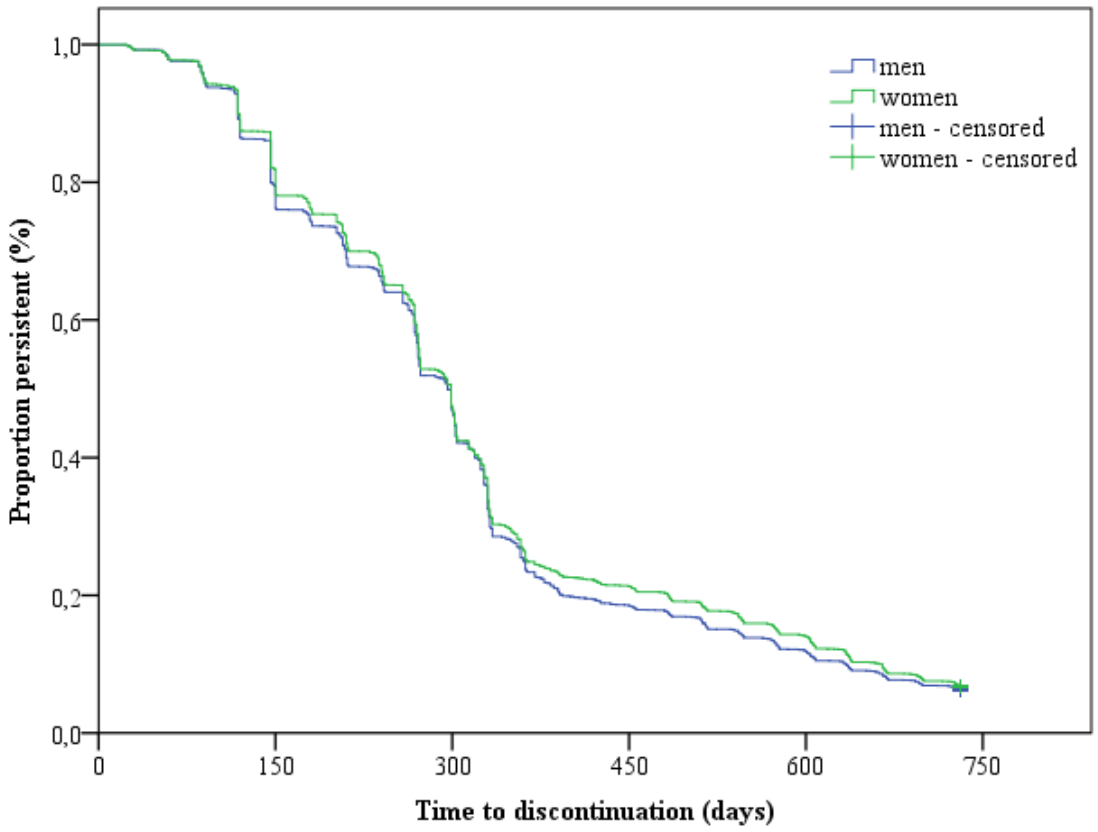

Figure 17. Persistence to AHT therapy, by gender

New users of AHT therapy, diagnosed and treated in the PHC units of Lisbon and Tagus Valley Region (n=8,856) during the 1st trimester of 2011. Crude estimates.

We also found differences in the proportion of persistent patients between age groups. Only 16 (1.8%) of younger patients (18 to 44 years) were classified as continuous users during the observation period while that proportion was 4.5 higher in older patients – 325 (8.2%) of patients aged 65 years or more were continuous users of AHT therapy during the two-year observation period (Figure 18). The differences between age groups was found out significant ($p<0.001$).

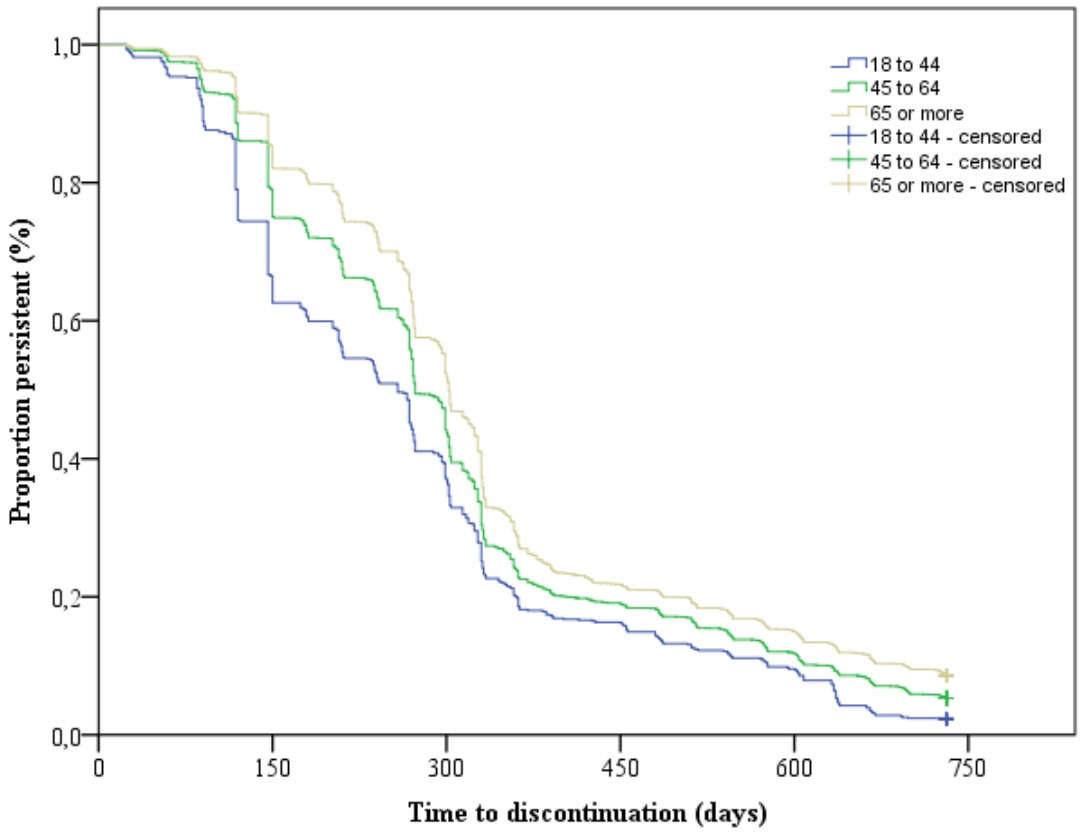

Figure 18. Persistence to AHT therapy, by age group

New users of AHT therapy, diagnosed and treated in the PHC units of Lisbon and Tagus Valley Region (n=8,856) during the 1st trimester of 2011. Crude estimates.

Discontinuation rates were lower in the LMA, compared to the rural areas and the interior, although that difference was not statistically significant (p=0.129). Still, the higher discontinuation rate in patients living in municipalities with a higher buying power was statistically significant (p=0.034). Discontinuation rates were also lower for patients diagnosed with k87 ICPC-2 code (p=0.001) (Table 19).

Table 19. Two-year persistence to AHT therapy, by patient's characteristics

Patient's characteristics	Persistent	Non-persistent	*p*-value
Total	539 (6.1%)	8,317 (93.9%)	
Gender			p = 0.300
male	235 (5.8%)	3,817 (94.2%)	
female	304 (6.3%)	4,500 (93.7%)	
Age			p <0.001
18 to 44	16 (1.8%)	869 (98.2%)	
45 to 64	198 (4.9%)	3,829 (95.1%)	
65 or more	325 (8.2%)	3,619 (91.8%)	
Region (NUTS III)[a]			p = 0.129
Great Lisbon	319 (6.4%)	4,628 (93.6%)	
Setubal Peninsula	99 (6.2%)	1,486 (93.8%)	
Middle Tagus	24 (4.3%)	537 (95.7%)	
West	58 (6.2%)	872 (93.8%)	
Leziria West Coast	39 (4.7%)	787 (95.3%)	
Buying power			p = 0.034
<100	171 (6.0%)	2,672 (94.0%)	
[100-200[	320 (6.5%)	4,606 (93.5%)	
≥200	48 (4.4%)	1,039 (95.6%)	
ICPC-2 code[b]			p = 0.001
k86	416 (5.8%)	6,701 (94.2%)	
k87	48 (9.4%)	463 (90.6%)	

Legend: NUTS – Nomenclatura das Unidades Territoriais para Fins Estatísticos; ICPC-2 – International Classification for Primary Care, 2nd

[a] Data missing for 7 patients; [b] Data missing for 1,228 patients

Considering the initially dispensed AHT drug class, 143 (12.0%) of patients who started their treatment with two or more AHT drugs were still on treatment two-year after the index date, twice the overall persistence rates for all AHT drug classes (Table 20).

Table 20. Two-year persistence to AHT therapy, by drug classes

Drug classes	Persistent	Non-persistent	*p*-value
Total	539 (6.1%)	8,317 (93.9%)	
Single pill / monotherapy			p<0.001
Diuretics	25 (3.8%)	637 (96.2%)	
BBs	27 (5.9%)	427 (94.1%)	
CCBs	22 (6.4%)	323 (93.6%)	
ACEIs	72 (5.0%)	1,365 (95.0%)	
ARBs	70 (5.4%)	1,215 (94.6%)	
Other AHT	6 (6.0%)	94 (94.0%)	
Single pill / fixed combination			
ACEI – diuretic/CCB	56 (4.5%)	1,188 (95.5%)	
ARB – diuretic/CCB	111 (5.4%)	1,932 (94.6%)	
Diuretics	7 (7.7%)	35 (92.3%)	
Combination therapy			
2 or more ATC codes	143 (12.0%)	1,052 (88.0%)	

Legend: BBs – Beta-blockers; CCBs – Calcium channel blockers; ACEIs – Angiotensin converting enzyme; ARBs – Angiotensin receptor blockers; AHT – Antihypertensive; ATC code - Anatomical Therapeutic Chemical code

For patients who were treated with a single AHT drug (ATC code – 5th level), only 152 (3.6%) were classified as continuous/persistent users while that proportion was 3.0 higher (10.9%) for patients who received prescriptions for three or more AHT drugs (p<0.001). Worth mentioning is that this crude estimates are influenced by the fact that persistence was considered in terms of therapy persistence, meaning that the number of drugs during the observation period was cumulative, irrespectively of the new drugs being an addition or a substitution to the initially prescribed ones.

The number of prescribers involved in hypertension treatment of the cohort members was also associated with persistence to AHT. 183 (9.8%) of patients who received prescriptions for three of more physicians during the observation period had no grace period lower than 90 days while that proportion was just 4.5% for patients who received prescriptions of AHT drugs from a single physician (p<0.001).

The multivariate Cox regression analysis confirmed age, number of drugs dispensed during the observation period, and number of prescribers to be important factors associated with discontinuation of AHT therapy. Gender, ICPC-2 code, patient's buying power, and initial drug class had no significant association to discontinuation of AHT therapy after adjustments for all potential predictors (Table 21).

Table 21. Factors associated with discontinuation of AHT therapy

	Crude HR[a]	*p*-value	Adjusted HR[a,b]	*p*-value
Gender		0.021		0.192
Men	1 (ref)		1 (ref)	
Women	1.05 (1.01-1.10)	0.021	0.97 (0.92-1.02)	0.192
Age		<0.001		<0.001
18 to 44	1 (ref)		1 (ref)	
45 to 64	0.87 (0.80-0.94)	0.001	0.87 (0.79-0.95)	0.001
65 or more	0.78 (0.72-0.85	<0.001	0.78 (0.72-0.85)	<0.001
ICPC-2 code[c]		0.100		0.527
K86	1 (ref)		1 (ref)	
K87	0.92 (0.84-1.02)	0.100	0.97 (0.88-1.07)	0.527
Buying power		0.630		0.696
<100	1 (ref)		1 (ref)	
[100-200[	0.98 (0.93-1.03)	0.353	0.99 (0.94-1.05)	0.858
≥200	0.98 (0.91-1.05)	0.535	1.03 (0.95-1.12)	0.498
Number of Drugs		<0.001		0.001
one	1 (ref)		1 (ref)	
two	0.92 (0.87-0.97)	0.001	0.94 (0.89-0.99)	0.038
three or more	0.83 (0.78-0.88)	<0.001	0.88 (0.82-0.94)	<0.001
Prescribers		<0.001		<0.001
one	1 (ref)		1 (ref)	
two	0.84 (0.80-0.89)	<0.001	0.85 (0.81-0.90)	<0.001
three or more	0.74 (0.70-0.78)	<0.001	0.76 (0.71-0.81)	<0.001

Legend: NUTS – Nomenclatura das Unidades Territoriais para Fins Estatísticos; ICPC-2 – International Classification for Primary Care, 2nd edition; HR – Hazard ratio.

[a] Calculated with 95% CI; [b] Cox regression model, including all covariates studied; [c] data missing for 9 patients

Table 21. Factors associated with discontinuation of AHT therapy (continuation)

	Crude HR[a]	*p*-value	Adjusted HR[a,b]	*p*-value
Drug Classes		0.027		0.201
Diuretics	1 (ref)		1 (ref)	
Diuretics Comb	1.26 (0.99-1.60)	0.057	1.22 (0.95-1.56)	0.127
BBs	1.11 (0.98-1.27)	0.104	1.07 (0.93-1.23)	0.348
CCBs	1.06 (0.92-1.22)	0.431	1.06 (0.91-1.23)	0.493
ACEIs	1.02 (0.92-1.12)	0.752	0.98 (0.88-1.09)	0.725
ACEIs comb.	0.99 (0.90-1.10)	0.907	0.99 (0.89-1.11)	0.944
ARBs	1.07 (0.97-1.19)	0.196	1.02 (0.92-1.14)	0.706
ARBs comb.	1.03 (0.94-1.13)	0.507	1.00 (0.91-1.11)	0.945
Other AHT	1.37 (1.09-1.73)	0.008	1.39 (1.08-1.79)	0.010
Two or more	0.98 (0.88-1.08)	0.661	1.01 (0.91-1.14)	0.807

Legend: HR – Hazard ratio; BBs – Beta-blockers; CCBs – Calcium channel blockers; ACEIs – Angiotensin converting enzyme; AHT – Antihypertensive; ARBs – Angiotensin receptor blockers;

[a] Calculated with 95% CI, [b] Cox regression model, including all covariates studied.

6.3.4. Discontinuation and reinitiation of antihypertensive therapy

Although only 539 (6.1%) of the new users of AHT therapy we're classified as continuous users, the fact is that the large majority of patients (72.2%) actually reinitiated hypertension treatment after the first episode of discontinuation (90 days or longer without any AHT drug). This clearly demonstrates the dynamics of the medication adherence process, where patients' frequently stop and reinitiate their treatment.

Figure 19 demonstrates the proportion of persistent patients considering the absence (or not) of a grace period longer than 90 days.

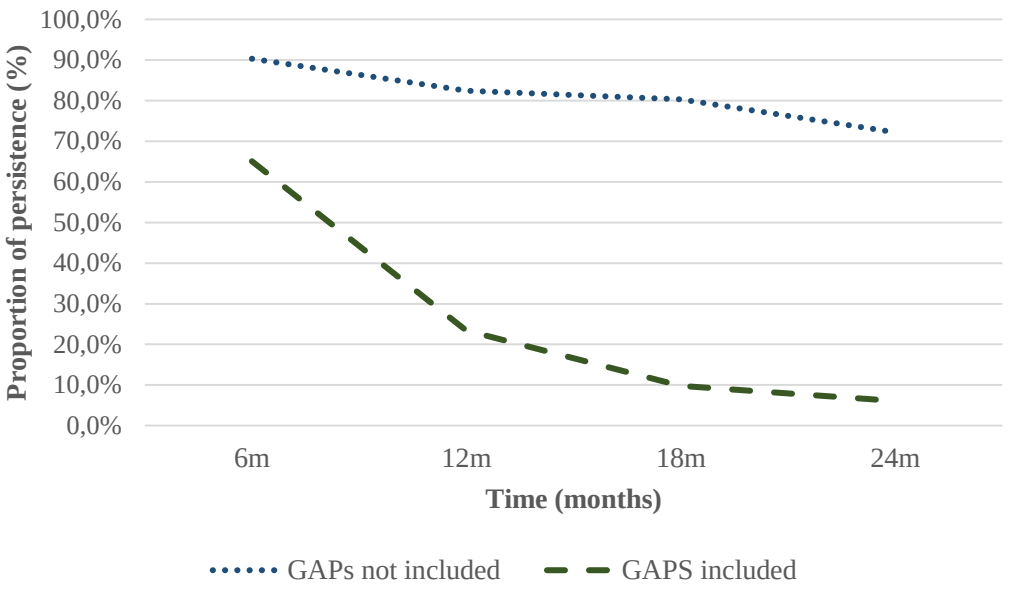

Figure 19. Persistence to AHT therapy considering the existence of a grace period of 90 days

Legend: New users of AHT therapy, diagnosed and treated in the PHC units of Lisbon and Tagus Valley Region (n=8,856) during the 1st trimester of 2011. Crude estimates. The blue line corresponds to the proportion of persistent patients taking in consideration only the end date of the last dispensing of an AHT drug, regardless the GAPs between dispensings. The green line corresponds to the proportion of persistent patients, including in the estimation of persistence rates, a grace period between dispensings lower than 90 days.

In this second analysis of persistence (where we included reinitiation of hypertension treatment, regardless a previous occurrence of one or more treatment gaps), we found that among the 8,856 new users of AHT therapy, 81.4% of men and 83.2% of women were still on treatment with at least one AHT drug 1-year after the index date. The proportion of patients still on treatment after two years dropped to 70.6% in men and 73.6% in women (Figure 20). The differences between men and women regarding persistence were statistically significant (p=0.002). Women had a higher persistence and the gender difference increased over time.

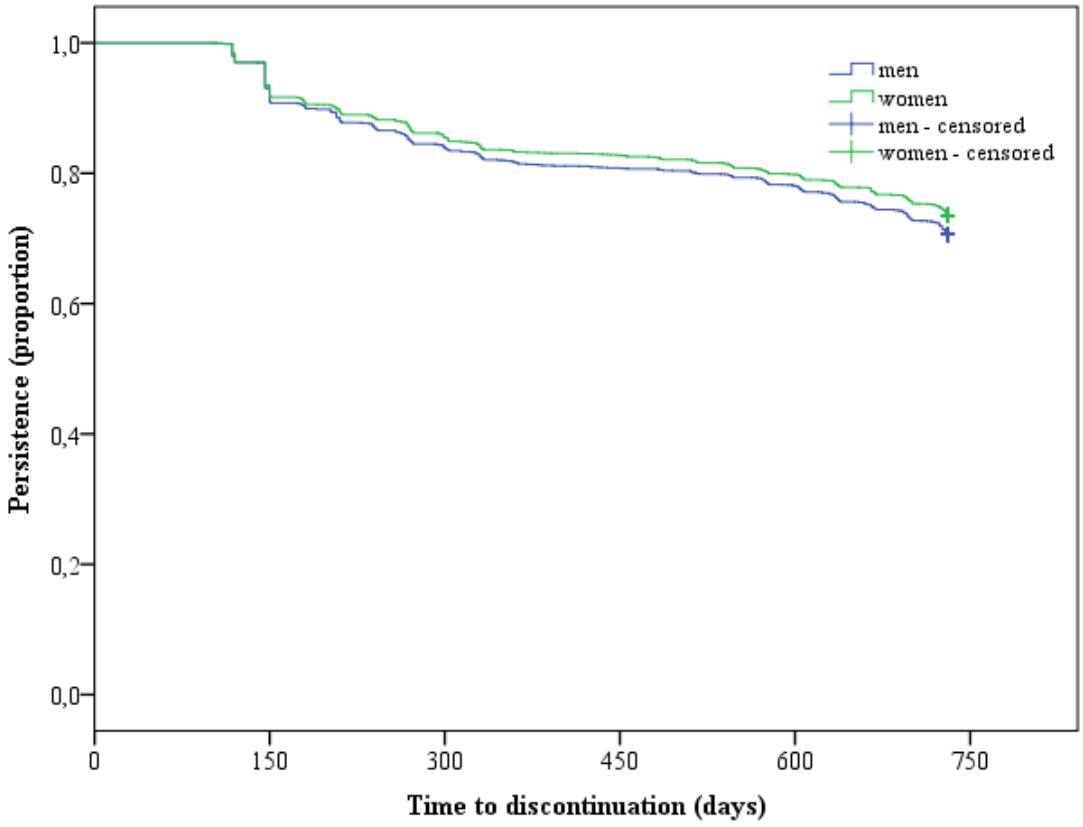

Figure 20. Persistence, including reinitiation, to AHT therapy by gender

New users of AHT therapy, diagnosed and treated in the PHC units of Lisbon and Tagus Valley Region (n=8,856) during the 1st trimester of 2011. Crude estimates.

We also found differences in the proportion of persistent patients between age groups. Less than half (48.5%) of younger patients were no longer on treatment two years after initiation, while 79.4% of older patients (65 years or more) still were. In terms of discontinuation rates, younger patients had a 2.5 times higher discontinuation rate than older patients (Figure 21). The differences between age groups was found out significant ($p<0.001$).

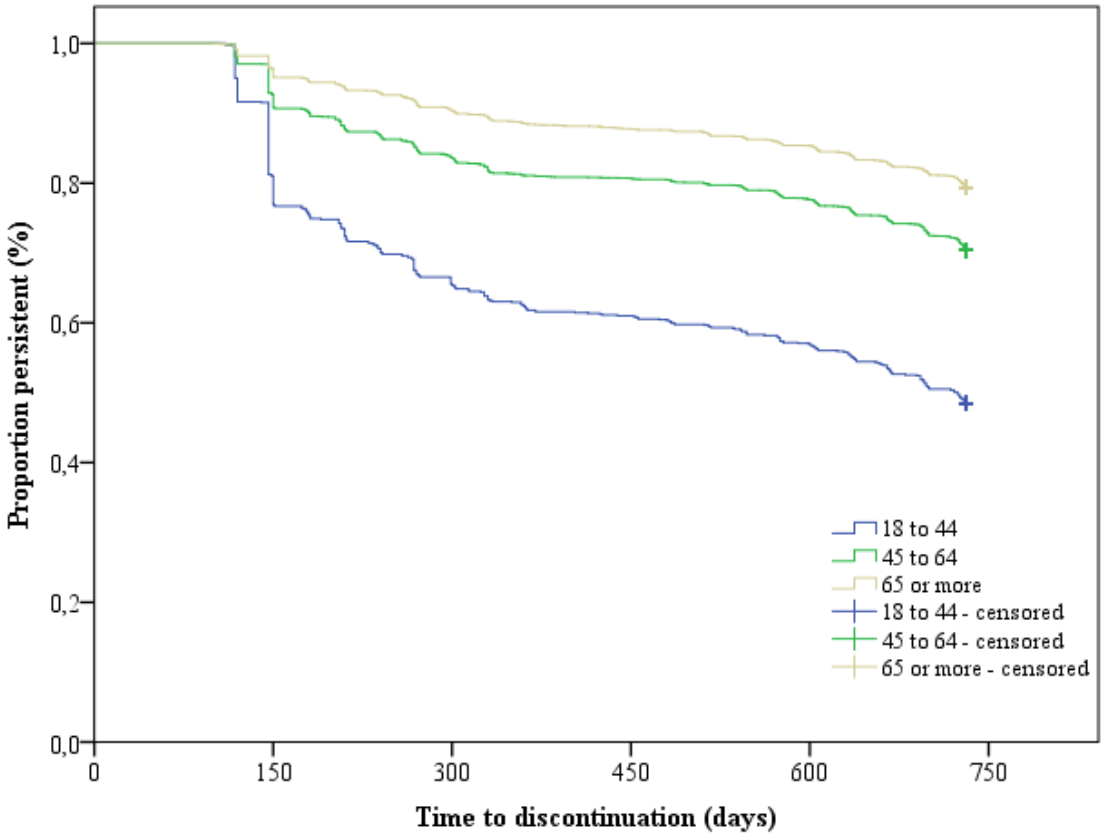

Figure 21. Persistence, including reinitiation, to AHT therapy by age group

New users of AHT therapy, diagnosed and treated in the PHC units of Lisbon and Tagus Valley Region (n=8,856) during the 1st trimester of 2011. Crude estimates.

Discontinuation rates were lower in the LMA, compared to the rural areas and the interior (p=0.006). The higher discontinuation rate in patients living in municipalities with a higher buying power was not statistically significant. Discontinuation rates were also lower for patients diagnosed with k87 ICPC-2 code (p=0.012) (Table 22).

Table 22. Discontinuation and reinitiation of AHT therapy, by patients' characteristics

Patients' characteristics	Persistent	Non-persistent	*p*-value
Total	6,395 (72.2%)	2,461 (27.8%)	
Gender			p = 0.002
male	2,861 (70.6%)	1,191 (29.4%)	
female	3,534 (73.6%)	1,270 (26.4%)	
Age			p <0.001
18 to 44	429 (48.5%)	456 (51.5%)	
45 to 64	2,834 (70.4%)	1,193 (29.6%)	
65 or more	3,132 (79.4%)	812 (20.6%)	
Region (NUTS III)[a]			p = 0.006
Great Lisbon	3,621 (73.2%)	1,326 (26.8%)	
Setubal Peninsula	1,142 (72.1%)	443 (27.9%)	
Middle Tagus	373 (66.5%)	188 (33.5%)	
West	678 (72.9%)	252 (27.1%)	
Leziria West Coast	576 (69.7%)	250 (30.3%)	
Buying power			p = 0.123
<100	2,057 (72.4%)	786 (27.6%)	
[100-200[	3,581 (72.7%)	1,345 (27.3%)	
≥200	757 (69.6%)	330 (30.4%)	
ICPC-2 code[b]			p = 0.012
k86	5,254 (73.8%)	1,863 (26.2%)	
k87	403 (78.9%)	108 (21.1%)	

Legend: NUTS – Nomenclatura das Unidades Territoriais para Fins Estatísticos; ICPC-2 – International Classification for Primary Care, 2nd

[a] Data missing for 7 patients; [b] Data missing for 1,228 patients

Considering the initially dispensed AHT drug class, 1,497 (73.3%) of patients who started their treatment with an ARB in a fixed-dose combination with a diuretic or a CCB were still on treatment two-year after the index date, while only 294 (64.8%) of patients who started their treatment with a BB were still on treatment (Table 23).

Table 23. Discontinuation and reinitiation of AHT therapy, by drug classes

Drug classes	Persistent	Non-persistent	*p*
Total	6,395 (72.2%)	2,461 (27.8%)	
Single pill / monotherapy			
Diuretics	445 (67.2%)	217 (32.8%)	
BBs	294 (64.8%)	160 (35.2%)	
CCBs	243 (70.4%)	102 (29.6%)	
ACEIs	1,002 (69.7%)	435 (30.3%)	
ARBs	925 (72.0%)	360 (28.0%)	
Other AHT	61 (61.0%)	39 (39.0%)	p<0.001
Single pill / fixed combination			
ACEI – diuretic/CCB	908 (73.0%)	336 (27.0%)	
ARB – diuretic/CCB	1,497 (73.3%)	546 (26.7%)	
Diuretics	56 (61.5%)	35 (38.5%)	
Combination therapy			
2 or more ATC codes	964 (80.7%)	231 (19.3%)	

Legend: BBs – Beta-blockers; CCBs – Calcium channel blockers; ACEIs – Angiotensin converting enzyme; ARBs – Angiotensin receptor blockers; AHT – Antihypertensive; ATC code - Anatomical Therapeutic Chemical code

For patients who were treated with a single AHT drug (ATC code – 5th level), 1,682 (39.9%) were no longer in treatment two-year after initiation, while for patients treated throughout the observation period with three or more AHT drugs, only 229 (11.2%) discontinued completely their hypertension treatment two-year after the index date significant (Figure 22). These differences were statistically significant (p<0.001).

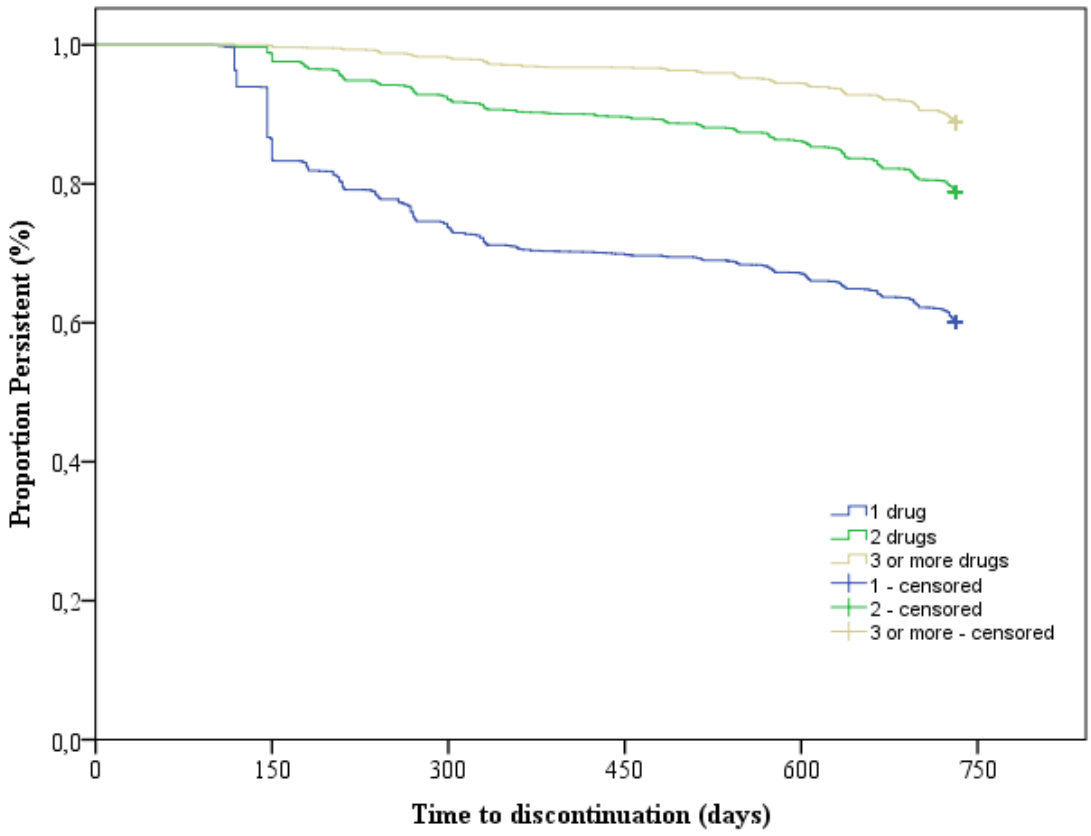

Figure 22. Persistence, including reinitiation, to AHT therapy considering the number of dispensed drugs

New users of AHT therapy, diagnosed and treated in the PHC units of Lisbon and Tagus Valley Region (n=8,856) during the 1st trimester of 2011. Crude estimates.

The number of prescribers involved in hypertension treatment of the cohort members was also associated with discontinuation of AHT. Patients who received prescriptions for three of more physicians during the observation period had lower discontinuation rates than patients who received prescriptions of AHT drugs from a single physician (92.3% *vs* 58.7%; chi-square test, $p<0.001$).

The multivariate Cox regression analysis confirmed age, region, number of drugs dispensed during the observation period, number of prescribers, patient's buying power, and initial drug class to be important factors associated with complete discontinuation of therapy. Gender, and ICPC code had no significant association to discontinuation rates after adjustments for all potential predictors and therefore were not included in the model (Table 24).

Table 24. Factors associated with discontinuation, including reinitiation, of AHT therapy

	Crude HR[a]	*p*-value	Adjusted HR[a,b]	*p*-value
Gender		0.002		0.280
Men	1 (ref)		1 (ref)	
Women	0.89 (0.82-0.96)	0.002	0.95 (0.87-1.04)	0.280
Age		<0.001		<0.001
18 to 44	1 (ref)		1 (ref)	
45 to 64	0.47 (0.42-0.52)	<0.001	0.51 (0.45-0.57)	<0.001
65 or more	0.31 (0.27-0.34)	<0.001	0.31 (0.28-0.36)	<0.001
ICPC-2 code[c]		0.008		0.204
K86	1 (ref)		1 (ref)	
K87	0.77 (0.63-0.93)	0.006	1.14 (0.93-1.38)	0.204
Region (NUTS III)[d]		0.005		<0.001
Middle Tagus	1 (ref)		1 (ref)	
West	0.77 (0.64-0.93)	0.007	0.83 (0.67-1.03)	0.094
Setubal Peninsula	0.80 (0.68-0.95)	0.011	0.91 (0.74-1.11)	0.337
Leziria West Coast	0.87 (0.72-1.05)	0.139	1.06 (0.86-1.32)	0.566
Great Lisbon	0.76 (0.65-0.89)	<0.001	0.75 (0.61-0.92)	0.005
Number of Drugs		<0.001		<0.001
one	1 (ref)		1 (ref)	
two	0.44 (0.40-0.48)	<0.001	0.45 (0.40-0.50)	<0.001
three or more	0.22 (0.19-0.26)	<0.001	0.28 (0.23-0.33)	<0.001
Prescribers		<0.001		<0.001
one	1 (ref)		1 (ref)	
two	0.34 (0.31-0.38)	<0.001	0.34 (0.30-0.38)	<0.001
three or more	0.14 (0.12-0.17)	<0.001	0.16 (0.12-0.19)	<0.001
Buying Power		0.183		<0.001
<100	1 (ref)		1 (ref)	
100-200	0.98 (0.90-1.08)	0.720	1.22 (1.07-1.38)	0.002
>=200	1.10 (0.97-1.25)	0.140	1.60 (1.33-1.92)	<0.001

Legend: NUTS – Nomenclatura das Unidades Territoriais para Fins Estatísticos; ICPC-2 – International Classification for Primary Care, 2nd edition; HR – Hazard ratio.

[a] Calculated with 95% CI; [b] Cox regression model, including all covariates studied; [c] data missing for 7 patients; [d] data missing for 1,228 patients

Table 24. Factors associated with discontinuation, including reinitiation, of AHT therapy (continuation)

	Crude HR[a]	*p*-value	Adjusted HR[a,b]	*p*-value
Drug Classes		<0.001		<0.001
Diuretics	1 (ref)		1 (ref)	
Diuretics Comb	1.16 (0.82-1.66)	0.404	1.40 (0.95-2.08)	0.088
BBs	1.11 (0.90-1.36)	0.339	1.04 (0.83-1.30)	0.736
CCBs	0.87 (0.69-1.10)	0.245	1.22 (0.93-1.59)	0.148
ACEIs	0.90 (0.77-1.06)	0.214	0.90 (0.74-1.08)	0.261
ACEIs comb.	0.79 (0.66-0.93)	0.006	0.86 (0.71-1.05)	0.138
ARBs	0.84 (0.71-0.99)	0.038	0.76 (0.63-0.93)	0.006
ARBs comb.	0.78 (0.66-0.91)	0.002	0.82 (0.69-0.99)	0.033
Other AHT	1.28 (0.91-1.80)	0.159	1.67 (1.13-2.46)	0.009
Two or more	0.53 (0.44-0.64)	<0.001	1.21 (0.96-1.54)	0.109

Legend: HR – Hazard ratio; BBs – Beta-blockers; CCBs – Calcium channel blockers; ACEIs – Angiotensin converting enzyme; AHT – Antihypertensive; ARBs – Angiotensin receptor blockers; a) Calculated with 95% CI, b) Cox regression model, including all covariates studied.

6.3.5. Overview on the medication adherence process

At the end of this chapter, we found that of the 10,204 cohort members, 493 (4.8%) never acquired any AHT drug prescribed by a PHC physicians or any other physician and 855 more (8.4%) initiated hypertension treatment with a considerable delay (six-months or longer) after the first prescription.

Among patients with a first dispensing (n=8,856), 638 (7.2%) patients discontinued AHT therapy after being acquiring just the first prescription and 519 more (5.9%) completely discontinued treatment during the first year, making a total of 1,157 (13.1%) patients who were no longer on treatment at the end of the first year. During the second year, 904 (10.2%) more discontinued AHT therapy.

However, in spite of 6,157 patients were still on treatment two years after the initiation of hypertension treatment, only 539 (8.8%) of them were classified as continuous users, i.e. had no treatment gap or grace period of 90 days or longer, meaning that the remaining 5,618 (91.2%) were using AHT therapy in an ‘on and off’ basis, discontinuing and reinitiating it over time.

Analysing the implementation of hypertension treatment in the two-year observation period, among patients with a first dispensing only 456 (5.1%) had in their possession AHT drugs for 80% or more days, regardless the occurrence of lapses in implementation, i.e. treatment gap or grace periods of 90 days or longer, which occurred in 233 (51.1%) of this patients with a high level of implementation.

CHAPTER 7: DISCUSSION

DISCUSSION

In this chapter, starting from an overview of the relationship between non-adherence to AHT therapy and lack of BP control in the population, the results of this thesis are compared to the published literature on adherence to AHT therapy and put in perspective. The novelty of our findings but also this thesis limitations are discussed.

ADHERENCE TO ANTIHYPERTENSIVE THERAPY AND BLOOD PRESSURE CONTROL

Hypertension is the most common modifiable CV risk factor, and has been identified as the leading risk factor for mortality worldwide[1-3]. However, and in spite of advances in hypertension treatment in the second half of the 20th century, which have provided newfound capability for lowering BP in almost every person with hypertension, it continues to be a major public health problem whose prevalence is increasing worldwide.

Even though the percentage of patients with hypertension that are actually diagnosed has increased over time, the percentage of patients with controlled BP has not followed the same pattern, despite the therapeutic advances[4]. In spite of the consequences of uncontrolled hypertension being very well known among the general population, the vast majority of patients – approximately half to two-thirds[4]; 57.5% in the Portuguese population[16] – with hypertension still have inadequately controlled BP.

This means that there is room for improvement in the management of hypertension. Although the precise reasons for patients not achieving target BP despite being treated are not completely clear yet, still the literature was shown that non-adherence and non-persistence (discontinuation) of AHT therapy are perhaps the most important causes of poor BP control[6], which substantiates the importance of this thesis and its findings, leaving no doubt about the relevance of concerns about inadequate medication intake.

Thus, assessing adherence to AHT therapy in all of its components and the identification of potential risk factors for non-adherence within the Portuguese population are of major importance in planning preventive strategies aimed at improving BP control and, therefore, modifying the overall CV risk of the population.

RELEVANCE OF THIS THESIS

This thesis was conducted on a topic where there is a vast number of publications. However, there is also a wide range of terms used to define the act of acquiring prescribed medications and taking those prescribed medications appropriately. All this terms describe a deviant behaviour and are often used interchangeably, although defining different aspects of the medication-taking behaviour[25,105]. Even the methodological aspects vary immensely. For example, in the absence of any gold standard, Hess et al[160] identified 11 different methods for calculating adherence using pharmacy administrative databases.

Thus, the wide range of adherence and persistence (or discontinuation) rates in published studies is presumably a reflection not only of the number and complexity of reasons for deviant medication-taking behaviour[18] but also of the range of methodologies and AHT drugs that have been used in the conducted studies.

So, in this thesis we've considered the definition of adherence to medications as has been proposed by ABC Project: "the process by which patients take their medications as prescribed"[77]. As a (dynamic) process it consists of three components: initiation, implementation and discontinuation. The main implication of this definition is that adherence is not a therapeutic parameter that can be described by a single number, as usually reported in the literature.

However, quantification of adherence and interventions to its improvement have been largely conditional on patients acquiring their initial prescriptions, and have failed to accurately account for the component of initiation.

In a scoping review[180] we've conducted during December 2014 aiming to describe the scope (quantity, focus and nature) of published research on medication adherence in the Portuguese population, we found a lack of publications on initiation and discontinuation of hypertension treatment. We also found in that review that with the exception of the study published by Moita et al[42], all studies evaluated adherence at a local level, with

small samples of patients (range: 61 to 197 patients), therefore limiting the extrapolation of their results to the Portuguese population.

Additionally to the study conducted by Moita et al[42] aiming to characterize the adherence behaviour to ARBs of hypertensive patients living in Alentejo, one other study was recently published where primary (non-)adherence was evaluated in the Portuguese population (a cross-sectional study undertaken in the community pharmacies of the LMA between March and April 2012)[41]. In both studies, primary adherence was defined as the ratio between dispensed and prescribed drugs, not differentiating between newly treated patients and ongoing/established users of AHT therapy.

Although sometimes used in the literature interchangeably, primary adherence and initiation are not necessarily synonyms, and so we've evaluated both aspects of the medication-taking behaviour, which was an innovate feature of this thesis.

In this context, and to the best of our knowledge, this was the first study in Portugal to determine adherence including the three components of the adherence process – initiation, implementation and discontinuation/persistence – for AHT therapy. All previous studies, with the aforementioned exceptions[41-42], focused only in the implementation component, by analysing adherence within ongoing/established users[35-40].

This was also an innovative feature of this thesis because the determinants of adherence are not the same for initiation, implementation and discontinuation. For example, our results show that in spite of men demonstrated higher initiation and implementation rates than women, women demonstrated higher persistence than men. Not all of this findings were statistically significant, but they demonstrate that the same risk factor may influence adherence in a different manner overtime.

We also have to consider that one patient's determinants of adherence can change over time, for example, the beliefs of the patient concerning his/her disease and his/her trust in the therapy can evolve[25;128]. Thus, the prediction of non-adherence for individual patients is therefore difficult. That's why measurements of the three elements of adherence are required to established multifaceted interventions to improve adherence.

Also, an innovative feature of our thesis was the use of prescriptions and dispensing/claims records for quantification of adherence to the wide array of AHT drugs. The study conducted by Moita et al[42] evaluated only to ARBs and all the other studies on adherence to AHT therapy in Portugal were cross-sectional (therefore, not allowing estimation of how long medications are used) and evaluated adherence using questionnaires as the main source of information[35-41], a more prone to error method, easily distorted by patients[23,25].

ADHERENCE TO ANTIHYPERTENSIVE THERAPY IN THE LISBON AND TAGUS VALLEY REGION: MAIN FINDINGS

The results of this thesis confirm previous observations[62-63,66,86,91-92,115] that in clinical practice hypertension treatment is frequently abandoned and poorly implemented over time.

In this population, almost one out of five (19.5%) patients either never initiated treatment, did it with a considerable delay (after six months or more after receiving a first prescription for at least one AHT drug) or completely discontinued it just after acquiring their first prescription. Overall, only 539 (8.8%) of patients that were still on treatment two years after initiating hypertension treatment, were classified as continuous users, i.e. had no episode of discontinuation. The remaining patients either completely discontinued their treatment or implemented it on a 'on and off' basis, which was reflected on a very low proportion of patients (5.1%) classified as having a high level of implementation.

We found that the risk of completely discontinuing all AHT therapy was most pronounced during the first year, which is consistent with other studies findings[28,91,95,115], where it has been demonstrated that discontinuation rates are likely to be higher during the first year of follow-up but are more likely to remain rather stable thereafter for the long term.

Possible reasons might have been uncertainty about whether or not real hypertension existed and the appearance of adverse drug effects. In fact, the literature shows that sub optimal adherence is partly due to the asymptomatic nature of hypertension[56,67,128,130]. Due to that fact, during hypertension treatment patients may experience no symptom relief and experience more side-effects while taking their medications correctly. The use of diuretics was associated with one of the lowest primary adherence rates and also with complete discontinuation and of AHT therapy, just like BBs (only drug class, not considering the 'other' AHT class, with an early discontinuation rate over 10%), which were possibly due to increased adverse effects of drugs from this drug classes, as found by other authors[107,128].

Overall, and concerning the impact of drug class on adherence to AHT drugs, our results are consistent with the meta-analysis conducted by Kronish et al[19], where the authors demonstrated superior adherence to ARBs and ACEIs and inferior adherence to diuretics. ARBs seem to be associated with placebo-like tolerability[175], with lower adverse effects reported compared to other AHT drug classes[50].

However, it is a matter of concern if many patients needing AHT therapy stop their treatment during the first months after treatment initiation. In our study, persistence (not considering treatment reinitiation) was lower compared with other studies[59,93-95,121]. In a general practice study in the UK, one in two patients had discontinued all AHT therapy by 3 years post-treatment initiation[95]. In a Sweden study using medical records for patients with hypertension in 48 Swedish PHC centres, persistence after two years was 65%[121] and in a German study persistence after four years ranged from 27% for diuretics to 34% to CCBs[94]. In a Norwegian study analysing persistence after four years, two-thirds of the initial users of thiazides and ARBs were persistent users after four years[59].

However, in those studies, the definition of persistence is not the same. Still, as persistence dissimilarities between countries are pronounced, it is unlikely that they are due to different definitions alone. In this thesis, low persistence rates with AHT therapy and the differences must lead us to pay some attention to the functioning of our healthcare system. In fact, we cannot rule out the possibility that patients may acquire AHT drugs in a community pharmacy without a medical prescription. Although all

AHT drugs are classified as ‘prescription required’, it is known that patients sometimes acquire them without a prescription. A study published in the June 2015 journal of the Portuguese consumers association (DECO Proteste) shown that 14% of the study responders had already bought a drug classified as ‘prescription required’ in a pharmacy. Therefore that may imply that we’ve had overestimate not just discontinuation rates but also the implementation of AHT therapy.

On this matter, in this thesis we found a higher risk of complete discontinuation of AHT therapy, even taking in consideration a possible reinitiation over time, for patients with the highest buying power (HR=1.60; CI: 1.33-1.92). This finding might be a consequence of patients acquiring AHT drugs without a medical prescription. In this case, patients with a higher buying power could more easily afford to pay the RRP of the drug than patients with a lower buying power, therefore, having to require a prescription for the family doctor or other physician to acquire AHT drugs. Further research will be needed to demonstrate exactly how much AHT drugs are dispensed in pharmacies without a prescription.

Our results also show that younger patients were more likely to completely discontinue their treatment, after the first dispensing or during the two-year observation period. In fact, almost one out of five patients under 45 years interrupted their hypertension treatment after the first dispensing. Different factors may play a role in this decision: as we already mentioned, it’s well known that the asymptomatic nature of hypertension reduces patient motivation to take the drugs as prescribed[56,67,128,130], which might be more relevant for younger patients; also this patients may adhere to appropriate lifestyle changes that have a positive impact on the evolution of the disease and therefore, reduce the need of medications. Finally, early and long term discontinuation can reflect adverse events of AHT drugs. In fact, the study conducted by Cabral e Silva[82] demonstrated that the main reasons for non-adherence related to the drugs themselves were adverse events and symptomatic improvement followed by discontinuation.

Looking to the primary adherence rate of AHT drugs prescribed by PHC physicians, we found that 41.5% of all prescribed AHT drugs were not purchased by the patients. Overall, the rate of primary adherence we’ve calculated reflects what already was known from studies conducted in other population-based studies using pharmacy refill

rates: patients typically obtain less medication than they have been prescribed[30,42,75]. Restricting the analysis to ARBs, the rate of primary adherence was much similar to the rate calculated by Moita et al[42] to ARBs in the Alentejo Health Region in the years 2010-2011, using the same methodology, which was 61.2%.

Even if we didn't account for all prescribed packages and counted every prescription record as a single package the primary adherence rate would be 69.7%. Still, that would mean that over 30% of all prescribed drugs were not acquired by patients.

Thus, our results present a considerably lower primary adherence rate (or a higher primary non-adherence rate) compared to other studies. Fischer et al[102] evaluated 195,930 e-prescriptions for different drug classes and for AHT drugs found a primary non-adherence rate of 19.5% for AHT drugs. Ax and Ekedahl[174] evaluated 44,607 e-prescriptions in a Swedish population and found a non-adherence rate of just 2.5%. Karter et al[108] identified 5% primary non-adherence, and Raebel et al[113] 7%. Cooke[112] found that 15.6% of new prescriptions for AHT drugs were never acquired by patients. Shah et al[103] found that 17% of prescriptions that were written for AHT drugs were never purchased at community pharmacies.

However, studies conducted in Portugal regarding primary (non-)adherence reflect much similar rates to our ones. For example, the study conducted by Moita et al[42] revealed that primary adherence stood at 61.2%. Costa et al[41], in the previously mentioned cross-sectional study undertaken in the LMA identified 22.8% of patients as non-adherent. However, data was collected from patients that actually went to the pharmacy and didn't acquire all prescribed drugs, which in the literature has been called *abandoned* prescriptions[107,174]. This means that were also other prescriptions written by the physicians that were not delivered to the pharmacy, which may indicate a sub estimation of primary non-adherence.

Medication-taking behaviour is extremely complex and individual, and influenced by multiple factors; no less than 771 individual risk factor items were identified as being associated with adherence to long term treatment[128].

Numerous studies[56;65-66,102,110-112,131-132] found that increased out-of-pocket costs are associated with decreased use of prescribed medications, even for highly effective ones, such as AHT, which was also found in this thesis not just for primary adherence rate, but also for treatment initiation and early discontinuation.

However, and as we've described in chapter two, the higher rate of adherence to ARBs compared with diuretics, for example, suggests that drug cost plays a relatively minor role in AHT adherence. Actually, when adjusted with other potential risk factors for initiation, we found no statistically significant association between out-of-pocket cost and initiation of AHT therapy.

Moreover, we found no differences in the primary adherence rates of prescribed generic or brand name drugs (p=0.710). Also, there were no differences on the rate of initiation and on the rate of early discontinuation between generic and brand name drugs (86.1% *vs* 85.6; p=0.497 and 8.7% *vs* 8.4%; p=0.569, respectively). The availability of generic forms of most AHT drugs seems to mitigate the impact of out-of-pocket cost on adherence, as demonstrated by other authors[103;107]. This finding is also in line to previous studies[107,133,182] on the impact of generic AHT drugs on medication adherence.

Also, our findings support the fact that the use of low-dose combinations favours adherence probably because of the smaller side effects compared to full-dose therapy[5,63,138], and also because it reduces the complexity of therapy.

Unmeasured patient and physician factors, such as the extent of physician–patient communication and education about prescriptions are likely to influence adherence, as shown in the literature. Still, in this thesis, we've found slightly higher primary adherence rates when the drug was prescribed by the patient's family doctor, although such differences were not statically significant. Also, initiation and early discontinuation rates were not influenced by that fact, implying that in this population that is not an important risk factor for non-adherence.

Although individuals at low socioeconomic status have sometimes been reported to have a lower adherence to treatment[11,67,128,130,181], in this thesis, patients with higher buying power demonstrated higher discontinuation rates, just like in the study

conducted by Corrao et al[62] in the Lombardy (Italy) population. However, those differences were not statistically significant for early discontinuation (p=0.439), and after adjustment to other predictors of discontinuation, it was associated with discontinuation of AHT therapy (p=0.696) meaning that in the Lisbon and Tagus Valley population, implementation and/or discontinuation of AHT therapy is not related to the socioeconomic status. However, and as we've mentioned, if we account for reinitiation in the definition of persistence, higher buying power increased the risk of discontinuation.

METHODOLOGICAL CONSIDERATIONS

While trying to assess the clinical relevance of inadequate medication-taking behaviour, we have to consider several aspects of non-adherence with chronic medication. Without doubt, non-adherence with any form of chronic treatment generally means less protection against worsening of symptoms or protection against the occurrence of complications.

However, this raises a question often posed when it comes to adherence namely "how much adherence is enough?" There is no mutual agreement among health care professionals about what adequate adherence is. As we've mentioned, a ratio of 80% is often accepted as cut-off value between adherent and non-adherent in AHT treatment research. Several studies, carried out in PHC settings and using medication records for adherence calculations, in which the effect of non-adherence on clinical outcomes was investigated, have demonstrated that an adherence level of approximately 80% may already be sufficient for a satisfying BP[62-64,176].

For some drugs with a long half-life or with extended release formulations, missing a dose may be less clinically relevant (forgiving drugs), although non-adherence still reflects unwanted behaviour[178-179]. From a pharmacological point of view, we could even argue that missing one dose will have limited or no pharmacodynamics consequences. It is, in fact, the plasma half-life of AHT drugs that determines whether a pharmacodynamic effect persists when a patient misses a single dose. Despite these

considerations, it remains difficult to define an adherence level that is absolutely necessary for reaching adequate BP reduction.

Nevertheless, it seems obvious that allowing a patient missing a dose now and then or even allowing longer periods of missing doses (i.e. drug holidays), is acceptable if it means that the patient is prepared to continue the use for years. Missing one or perhaps even a few doses may have no demonstrable effect on outcome. As Corrao et al[62] have demonstrated, not just an optimal (80% or more of doses), but even a suboptimal or partial adherence to AHT therapy may offer significant advantages, compared with an extremely low adherence (less than 40% of doses).

In case of individual AHT drugs or even AHT drug classes, it is impossible to even suggest an overall cut-off value for clinically relevant non-adherence. However, if rebound effects are absent or unlikely to occur, it seems irrelevant to strive for perfection and in this light 80% seems an acceptable limit. In addition, this cut-off value can also be recommended in new studies, because it enables comparison between studies and is the most frequently used cut-off value in pharmacoepidemiology[26].

Also important to consider is the fact that MPR is the accepted standard for the evaluation of adherence using retrospective data[26,34,105]: it is 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 AHT therapy using retrospective data[34,105].

Another problem addressed in this thesis is the definition of persistence. We already addressed the problem of defining adherence with regard to the frequently used cut-off value of 80%. The same problem may be encountered with regard to non-persistence. A large number of studies on persistence with AHT drugs have been performed using different definitions. When studying persistence, instead of defining a cut-off value, which is the case with adherence, we have to define when a gap between two prescriptions is so large that continuous use can no longer be assumed. Therefore, setting the cut-off for that maximum medication gap is equivalent to define the sensitivity of the measure because the smaller the allowable gap, the higher the number of patients classified as having discontinued or being non-persistent. A 90-day gap might be adequate to detect true non-persistence because a study investigating the

impact of several gap selections on persistence observed no major change with increasing gap days >90 days[85]. It is also the most common gap used in hypertension persistence studies[62,85,91,93-95,121].

LIMITATIONS OF THIS THESIS

Naturally, this has a number of potential limitations, most of them related to the method used for estimating adherence to AHT therapy, i.e. the use of medication records, namely an electronic prescriptions database as well a pharmacy dispensing/claims database.

The use of medication records is the most feasible and widely used source of information to estimate adherence in large populations[26,84,105]. Additionally prescription and dispensing/claims (refill) databases have been considered the *gold standard* method for initiation measurement if both databases are combined[118], which as we've demonstrated can be done within SIARS, and also for discontinuation, with the limitation of being retrospective.

Medication records are increasingly collected worldwide and available from different sources such as prescribing, dispensing, or reimbursement databases. The ready availability of these records has stimulated widespread use of these data to study patterns of medication use and assess medication adherence in daily clinical practices[31,33,105]. Calculations with medications records represent a simples approach to determine how much of the prescribed medications are being taken (i.e. adherence) and for how long (i.e. persistence). They are objective, non-invasive, and economical for use in large populations because they can be easily derived from data routinely collected for administrative or other purposes, such as the case of SIARS.

In fact, the construct of medication adherence comprises a set of inter-related health behaviours. One of such behaviours, the act of acquiring a prescribed medication, can be estimated objectively using electronic databases such as pharmacy dispensing and/or claims databases[101].

Over the last years, advances in electronic prescribing have expanded the ability to assess whether or not patients obtain their initial prescriptions, the first component of the medication adherence process[25,101]. As we've demonstrated with our results, electronic prescribing allowed the possibility to identify cohorts of patients who have been prescribed new drugs and determine whether those drugs were ever dispensed, were acquired only once or more, were used as prescribed, or subsequently discontinued without clinical advice or recognition[108].

However, while using medication records for estimation of adherence to medications, some assumptions have to be made.

First of all, we have to assume that medication records are complete, comprehensive, and accurate. In our case, although data collected from SIARS have not been subject to previous validation, the drug claims database is a highly accurate data source because community pharmacies have to submit error free claims for reimbursement of the government funded components of dispensed drugs, otherwise they won't receive that reimbursement.

Secondly, the assumption that the first intake occurred on the day of the first acquisition, which may not be case. Also, the assumption has to be made that the theoretical duration of an individual dispensed drug corresponds to the actual drug use, i.e. the medication is taken as indicated, which may also not be invariably the case. This means that dispensing/claims records were used as a proxy for actual medication taking process, even though a prescription acquisition is not equivalent to ingestion of the drug. However, it can be reasonable assumed that patients would not continue to refill a prescription without the intention to adhere.

Other assumptions underlying adherence measures with medication records include (i) lack of a refill equals a medication not consumed after the oversupply is exhausted, i.e. medication has been discontinued; (ii) medications are not purchased or borrowed from another person or venue and finally, (iii) no unknown treatment interruptions or dosing changes occurred during the observation period.

By assuming that lack of a refill equals a medication not being consumed, 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. In fact, the use of medication records does not make it possible to determine whether discontinuation was prescriber-initiated or patient-initiated or even if the patient obtained his medication from sources not captured in the available data, such as sharing medication with others, like family members, and/or obtaining medication directly from a pharmacy, without a prescription. That's why we have to assume that medications are not purchased or borrowed from another person or venue. In this situations, non-adherence and/or non-persistence may be overestimate.

As we've previously demonstrated in this chapter, in our country, AHT drugs can be acquired in a community pharmacy without a medical prescription. The Pharmaceutical Good Practices for community pharmacy[183] include the possibility of an emergency dispensing depending on the evaluation and dispensing of a medication that a patient requires in emergency conditions, which requires previous knowledge of the patient's pharmacotherapeutic profile. In this conditions, the dispensing does not match to a claim and, therefore, that information in not recorded in SIARS, which may overestimate non-adherence and non-persistence.

Other limitation of this thesis is that prescriptions records lack the indication for which AHT drugs were prescribed. With AHT drugs, there may be some uncertainty on the indication because they can also be prescribed for other medical conditions, such as angina pectoris, heart failure, cardiac arrhythmias, and other CV diseases. This could introduce several forms of bias. In studies like this, a relevant number of patients, who do not use AHT drugs for hypertension, can incorrectly be classified as non-adherent or non-persistence. This could lead again to an overestimation of the problem of non-persistence or non-adherence. To control for that, our cohort included only patients with prescription of AHT drugs and diagnosis of hypertension, expressed in k86 and k87 ICPC-2 codes. Still, we couldn't control for all patients' characteristics that may influence the drug choice.

However, different studies in multiple European countries have demonstrated that the majority (up to 80%) of AHT drugs prescriptions were indeed prescribed for hypertension related diagnoses[59,62,182].

Also, in this thesis, the six-month run-in period[1] in which we've identified prescriptions and/or claims records of AHT drugs (excluding those patients from the cohort) also allowed us reducing indication bias associated with the prescription of an AHT drug for other indications, even in the case of an actual hypertension diagnoses during the first trimester of 2011.

Also to consider, the absence of data on possible confounding factors, such as co-morbidities, actual socioeconomic status (and not just patient's buying power), severity of concomitant diseases, and other risk factors for CV diseases, might be a limitation in the evaluation of adherence to AHT treatment.

Another limitation concerns the lack of information on dosage regimen in the database. Relaying on days' supply information for estimation of MPR and also time to discontinuation 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 was determined by defining a standard dosing for each AHT drug and evaluating its appropriateness to clinical practice using a panel of clinicians from different specialties.

We found that the defined standard dosing was appropriate for 96.3% of AHT drugs, with highest agreement for drugs whose standard dosing was QD, and when where prescribed by a PHC physician.

For this thesis, we decided not to use the defined daily dose (DDD) for the calculation of the number of days supplied within each dispensing, since it does not necessarily reflect the recommended or PDD in AHT drug classes[158]. Therefore, using DDD in medication adherence studies may introduce misclassifications[159] because it may differ

[1] This six-month run-in period is recommended by Halpern[84] and it is commonly used in adherence studies analyzing new users of AHT therapy[34,63,65,102,139,184].

from the PDD of an individual patient, thus not reflecting its use in "real world"[158-159]. Defining a daily dose per drug and not per ATC code/active substance, as we've done allowed a more reliable estimation of adherence to medications using prescription and/or claims records.

Finally, and as Karter et al[108] pointed out, claims-based research is subject to misclassification because all prescriptions not captured in the claims database are considered not dispensed, yet there are other reasons for not capturing dispensings, such as system failure or malfunction of the prescribing software or still an accidental drug entry prescription by the physician during the consultation; another reason may be that in spite of the fact that it isn't highly common, some AHT drugs may be prescribed as needed and therefore, not dispensed by the patient at the pharmacy. Therefore primary non-adherence may be overestimated.

In spite of this limitations, the use of rates of prescription refills is an objective method to calculate both adherence (in its various components) and persistence with chronic therapy, which requires a closed pharmacy system – just like the one existing in our country, to improve its reliability.

Also, databases such as the ones we've used for this thesis provide an estimate of the highest possible level of medication possession and, thus, can identify those patients not able to consume the medication in sufficient quantity. In that sense, the measures can be considered to have a high sensitivity.

CONCLUSIONS

CONCLUSIONS

The main objective of this thesis was to determine adherence to AHT therapy in newly treated hypertensive patients in PHC units from Lisbon and Tagus Valley Health Region, in its three components – initiation, implementation and discontinuation.

Our results demonstrated some relevant findings. The first, is that almost one out of five (19.5%) patients either never initiated treatment, did it with a considerable delay (after six months or more after receiving a first prescription for at least one AHT drug) or completely discontinued it just after acquiring their first prescription.

A second relevant finding is that over a quarter of patients that actually initiated hypertension treatment completely discontinued it by the end of the second year.

A third important finding is that the large majority of patients implemented hypertension therapy on a 'on and off' basis, i.e. discontinuing (for a minimum period of 90) and then reinitiating it. This means that the decision to discontinue hypertension treatment is not definitive and therefore physicians should actively try to monitor adherence and discussing it with patients trying to identify restraints for the continuous use of the prescribed medications. Naturally, the effect of these types of interventions needs to be established in further studies.

Finally, a fourth finding of this thesis is that overall, almost one out of two prescribed AHT drugs were not dispensed (overall primary non-adherence rate = 41.5%), which was reflected in an average MPR of 43.6±23.1% (median 44.0%).

All of this findings combined, imply that the potential benefits of AHT therapy in lowering CV risk and the consequences of uncontrolled hypertension, cannot be fully realized in this population. Thus, the low adherence rates to AHT therapy, in all its components, is an especially alarming finding, since hypertension contributes greatly to the burden of mortality and morbidity from CV disease in Portugal.

Previous studies on adherence to AHT therapy in Portugal demonstrated higher adherence rates, compared to the ones found in this thesis. However, it is known that the

use of questionnaires and interviews to patients tend to overestimate adherence. Thus, our findings show a more clear landscape of the reality of adherence to AHT therapy in newly diagnosed and treated patients.

It has also previously been shown that in our country, many patients with hypertension either lack awareness of their diagnoses or are not receiving treatment[16]. Our findings demonstrated that even for patients receiving treatment, they either discontinue or poorly implement it over time.

So, non-adherence, in all its manifestations, translates into lack of BP control, which will ultimately also increase patients' risk of CV and related sequels and may lead physicians to assume inadequate effectiveness of the medication(s) being used and therefore adding or switching AHT drugs to hypertension treatment. As Cramer[69] pointed out, physicians should operate under the assumption that patients take approximately half of medications as prescribed, and therefore should look for non-adherence, as a reason for ineffectiveness of a treatment.

For all of this reasons, it has been suggested that increasing the effectiveness of methods for improving adherence may have a far greater positive impact on human health and its economics than any single improvement in medical treatment.

In that context, our results, may be instrumental for the development of interventions that encourage patients to initiate and use medications as prescribed, in a mutual agreement with the physician, leading to a full course of chronic therapy. Naturally, further research will be needed to confirm and better understand the causes of these findings and to develop interventions to improve adherence to AHT therapy, especially by the evaluation of other known risk factors unmeasured within this thesis and focusing on the individual patient's behavioural intentions, barriers and subjective norms. Since only a small fraction of the hypertensive population has an elevation of BP alone, with the majority exhibiting additional CV risk factors[6], adherence to AHT therapy should looked at by considering other drugs that the patients may be taking.

The medication-taking behaviour is extremely complex and influenced by hundreds of different determinants[17]. Determinants of non-adherence to AHT therapy such as the

long duration of therapy, symptomless nature of the disease, and medication related issues don't represent the full extent of risk factors for non-adherence. That's why further research must complement this population-based analysis with patient's perceptions about the disease and its treatment and patient's motivation and beliefs.

Also to considerer, the need to address the effect of lifestyle changes on BP control. The lowest implementation and discontinuations rates we found in this thesis for younger patients may be a result of the biasing effect of such changes, which are registered in databases like SIARS and therefore, may have confounded this study. In future observational studies, evaluation of lifestyle changes in a small subset of the population can help to estimate and adjust for the residual confounding resulting from the lack of information in SIARS.

Still, we have to consider that the literature shows that interventions aiming to improve adherence to AHT therapy have not demonstrated to be consistently effective in that intention[8,67]. Therefore interventions aimed at improving BP control must address the needs and challenges of patients in the various elements of the adherence process, especially for those who are first initiated on their prescribed drugs.

Overall, our results support the use of generic drugs and fixed-dose combinations for hypertension treatment. Also, our results reflect higher adherence rates for drugs acting on the RAS, compared to other AHT drug classes.

Finally, the benefits of using medication records not just for adherence evaluation but also to evaluate the effectiveness of interventions to improve adherence, cannot be ignored. These records results in better data sources and opportunities for real-time monitoring. Until recently, most of the evidence on medication adherence was based on follow-up studies of patients who have acquired their first prescription, underestimating the public health burden of poor medication adherence for newly prescribed drugs.

In our country, since 2010 electronic prescribing is mandatory for all NHS reimbursed drugs. This creates an electronic record of the written prescription, and so its use provides an opportunity to determine primary non-adherence of prescribed drugs, as well the rate of initiation of newly diagnosed and treated patients. Linking prescriptions

records to claims records also allowed determining whether AHT drugs were dispensed just once (early discontinuation), used as prescribed (implementation), or subsequently discontinued, therefore creating to measure adherence and persistence in a large population.

Worth mentioning is that for this thesis, only prescriptions records for the PHC units were available. So, our findings are relevant to patients newly treated in the setting of CV prevention and naturally, should only be applied to this specific population.

The integration of all prescription records, regardless the health care providing system in a single national prescriptions database will allow the escalation of this study and others like this to broader populations. Still, this thesis was based on data from a large unselected population, which was made possible by the fact that in Portugal, the NHS has universal coverage. So, reflect 'real world' data.

Despite the limitations, this thesis identified several determinants of adherence to AHT therapy in the Lisbon and Tagus Valley Health Region hypertensive patients that can provide insight into the development of strategies for early interventions. When prescribing AHT drugs, physicians should consider not only the benefits and risks of such drugs but also the different characteristics not just of the drug but also of the patient that may influence his/her adherence to medications.

REFERENCES

REFERENCES

1. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet 2005;365:217-23.
2. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2013;380(9859):2224–2260.
3. Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ. Selected major risk factors and global and regional burden of disease. Lancet 2002; 360:1347–60.
4. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al; and the National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High BP: The JNC 7 Report. Hypertension 2003;42:1206–1252.
5. Mancia G, De Backer G, Dominiczak A, et al; ESH-ESC Task Force on the Management of Arterial Hypertension. 2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension: ESH-ESC Task Force on the Management of Arterial Hypertension. J Hypertens 2007;25:1105–1187.
6. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, et al; 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;31(7):1281-357.
7. James PA, Oparil S, Carter BL, et al. 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311(5):507-520.
8. Schroeder K, Fahey T, Ebrahim S. Interventions for improving adherence to treatment in patients with high blood pressure in ambulatory settings. Cochrane Database of Systematic Reviews 2004, Issue 3. Art. No.: CD004804.
9. Sociedade Portuguesa de Hipertensão. Normas sobre Detecção, Avaliação e Tratamento da Hipertensão Arterial da Sociedade Portuguesa de Hipertensão. Rev Port Cardiol 2006;25(6):649-60.
10. Direção-Geral da Saúde. Hipertensão Arterial: definição e classificação. Direção-Geral da Saúde: Norma clínica n.º 20/2011. Atualização 19/03/2013.
11. Sabate E. Adherence to long-term therapies - Evidence for action. Geneva: World Health Organization, 2003.

12. Chobanian A. The Hypertension Paradox — More Uncontrolled Disease despite Improved Therapy. N Engl J Med 2009;361:878-87.
13. Chobanian A. Impact of Nonadherence to Antihypertensive Therapy. Circulation 2009;120:1558-60.
14. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological trials. BMJ 2009;338:b1665.
15. Psaty BM, Lumley T, Furberg CD, Schellenbaum G, Pahor M, Alderman MH, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. JAMA 2003;289(19):2534-44.
16. Polonia J, Martins L, Pinto F, Nazare J. Prevalence, awareness, treatment and control of hypertension and salt intake in Portugal: changes over a decade. The PHYSA study. J Hypertens 2014;32:1211–1221.
17. Brown MT, Bussell JK. Medication Adherence: WHO Cares? Mayo Clin Proc 2011;86(4):304-314.
18. Burnier M. Medication Adherence and Persistence as the Cornerstone of Effective Antihypertensive Therapy. Am J Hypertens 2006;19:1190–6.
19. Kronish IM, Woodward M, Sergie Z, Ogedegbe G, Falzon L, Mann DM. Meta-analysis: impact of drug class on adherence to antihypertensives. Circulation 2011; 123:1611–1621.
20. Cherry S, Benner J, Hussein M, Tang S, Nichol M. The Clinical and Economic Burden of Nonadherence with Antihypertensive and Lipid-Lowering Therapy in Hypertensive Patients. Value Health 2009;12(4):489-97.
21. Cramer JA, Rosenheck R, Kirk G, Krol W, Krystal J. Medication compliance feedback and monitoring in a clinical trial: predictors and outcomes. Value Health 2003;6:566-73.
22. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther 2001;23:1296-310.
23. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353(5):487-497.
24. Bramley, TJ, Gerbino, PP, Nightengale, BS, Frech-Tamas, F. Relationship of Blood Pressure Control to Adherence With Antihypertensive Monotherapy in 13 Managed Care Organizations. J Manag Care Pharm 2006;12(3):239-45.
25. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al; ABC Project Team. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol 2012;73(5):961-705.

26. Andrade S, Kahler K, Frech F, Chan K. Methods for evaluation of medication adherence and persistence using automated databases. Pharmacoepidemiol Drug Saf 2006;15:565–74.
27. Elliott WJ. Improving Outcomes in Hypertensive Patients: Focus on Adherence and Persistence With Antihypertensive Therapy. J Clin Hypertension 2009;11:376-82.
28. van Wijk BLG, Klungel OH, Heerdink ER, de Boer A. Rate and determinants of 10-year persistence with antihypertensive drugs. J Hypertens 2005;23:2101-7.
29. Blaschke TF, Osterberg L, Vrijens B, Urquhart J. Adherence to Medications: Insights Arising from Studies on the Unreliable Link Between Prescribed and Actual Drug Dosing Histories. Annu Rev Pharmacol Toxicol 2012;52:275–301.
30. Steiner JF, Prochazka AV. The Assessment of Refill Compliance Using Pharmacy Records: Methods, Validity, and Applications. J Clin Epidemiol 1997;50(1):105-16
31. Takahashi Y, Nishida Y, Asai S. Utilization of health care databases for Pharmacoepidemiology. Eur J Clin Pharmacol 2012;68:123–129
32. Wettermark B, Zoëga H, Furu K, Korhonen M, Hallas J, Nørgaard M, et al. The Nordic prescription databases as a resource for pharmacoepidemiological research—a literature review. Pharmacoepidemiol Drug Saf 2013;22:691–699.
33. Nielsen MW, Søndergaarda B, Kjøller M, Hansen EH. Agreement between self-reported data on medicine use and prescription records vary according to method of analysis and therapeutic group. J Clin Epidemiol 2008;61:919-924.
34. Krousel-Wood M, Holt E, Joyce C, Ruize R, Dornelles A, Webber LS, et al. Differences in cardiovascular disease risk when antihypertensive medication adherence is assessed by pharmacy fill versus self-report: the Cohort Study of Medication Adherence among Older Adults (CoSMO). J Hypertens 2015 Feb;33(2):412–420.
35. Morgado M. Desenvolvimento e avaliação de estratégias para aumentar a adesão à terapêutica farmacológica anti-hipertensora: Estudo da intervenção do farmacêutico hospitalar no controlo da pressão arterial. Covilhã. Tese [Doutoramento em Biomedicina] - Universidade da Beira Interior; 2011.
36. Silva J. Estudo da adesão à terapêutica farmacológica anti-hipertensora. Covilhã. Dissertação [Mestrado em Medicina] - Universidade da Beira Interior; 2013.
37. Ribeiro D. Adesão terapêutica e qualidade de vida em adultos e adultos idosos com hipertensão: fatores motivacionais. Porto. Dissertação [Mestrado em Psicologia] - Universidade do Porto; 2013.
38. Pinto AP. Viver com Hipertensão Arterial e Adesão ao Regime Terapêutico: Intervir para Prevenir. Beja. Dissertação [Mestrado de Enfermagem em Saúde Comunitária] – Instituto Politécnico de Beja; 2012.

39. Ferreira RS, da Graça LC, Calvinho MS. Adesão ao Regime Terapêutico de Pessoas com Hipertensão Arterial em Cuidados de Saúde Primários. Ver Enf Ref jan/fev/mar2016;8:7-15.
40. Lopes A. Avaliação da Adesão à Terapêutica em doentes com Hipertensão em Vila Franca de Xira. Faro. [Mestrado Integrado em Ciências Farmacêuticas] – Universidade do Algarve; 2013.
41. Costa FA, Pedro AR, Teixeira I, Bragança F, Silva JA, Cabrita J. Primary non-adherence in Portugal: findings and implications. Int J Clin Pharm 2015;37:626-635.
42. Moita B, Robalo J, Duarte A, Santana R. A utilização de fontes administrativas de dados na estimação da adesão terapêutica aos antagonistas dos recetores da angiotensina. Rev Port Saúde Pública. 2016;34(1):20-29.
43. World Health Organization. Global burden of disease. Geneva: WHO Press; 2008
44. Macedo ME, Lima MJ, Silva AO, Alcântara P, Ramalhinho V, Carmona J. Prevalência, Conhecimento, Tratamento e Controlo da Hipertensão em Portugal. Estudo PAP. Rev Port Cardiol 2007;26(1):21-39.
45. Uva MS, Victorino P, Roquette R, Machado A, Dias CM. Epidemiological research on the incidence and prevalence of hypertension in the Portuguese population: A scoping review. Rev Port Cardiol 2014;33:451-63.
46. Stampfer MJ, Ridker PM, Dzau VJ. Risk Factor Criteria. Circulation 2004; 109:IV-3-IV-5
47. Direção-Geral da Saúde. Avaliação do Risco Cardiovascular SCORE (Systematic Coronary Risk Evaluation). Direcção-Geral da Saúde: Norma n.º 05/2013. Atualização 26/11/2013.
48. World Health Organization. Prevention of cardiovascular disease: guidelines for assessment and management of total cardiovascular risk. 2007.
49. Direção-Geral da Saúde. Abordagem terapêutica da Hipertensão Arterial. Direcção-Geral da Saúde: Norma clínica n.º 26/2011. Atualização 19/03/2013.
50. Munger, MA, Van Tassell, BW, LaFleur, J. Medication Nonadherence: An Unrecognized Cardiovascular Risk Factor. Med Gen Med 2007;9(3):58.
51. Lawes CMM, Vander Hoorn S, Law MR, Elliott P, MacMahon S, Rodgers A. High blood pressure. In: Ezzati M, Lopez AD, Rodger A, Murray CJL, eds. Comparative quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors. Volume 1. Geneva, Switzerland: World Health Organization; 2004:281-389.
52. Franco OH, Peeters A, Bonneux L, de Laet C. Blood pressure in adulthood and life expectancy with cardiovascular disease in men and women. Hypertension 2005;46:280-6.

53. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). J Am Med Assoc 2002;288:2981–2997.
54. Kjeldsen SE, Hedner K, Julius S, Haley WE, Zabalgoitia M, Butt AR, et al. Hypertension Optimal Treatment (HOT) Study: Home Blood Pressure in Treated Hypertensive Subjects. Hypertension 1998;31:1014-1020.
55. World Health Organization. Joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Diseases. 2002. Report No. 916.
56. Chowdhury R, Khan H, Heydon E, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. Eur Heart J 2013;34:2940-8.
57. Cortez-Dias N, Martins S, Belo A, Fiúza M em nome dos investigadores do Estudo VALSIM. Prevalência e Padrões de Tratamento da Hipertensão Arterial nos Cuidados de Saúde Primários em Portugal. Resultados do Estudo VALSIM. Rev Port Cardiol 2009;28(5):499-523.
58. Gehi AK, Ali S, Na B, Whooley MA. Self-reported medication adherence and cardiovascular events in patients with stable coronary heart disease: the Heart and Soul Study. Arch Int Med 2007;167:1798-1803.
59. Selmer R, Blix HS, Landmark K, Reivkam A. Choice of initial antihypertensive drugs and persistence of drug use – a 4-year follow-up of 78,453 incident users. Eur J Clin Pharmacol 2012;68:1435-1442.
60. Laufs, U, Rettig-Ewen, V, Böhm, M. Strategies to improve drug adherence. Eur Heart J 2011;32(3):264-268.
61. DiMatteo MR, Giordani PJ, Lepper HS, Croghan TW: Patient adherence and medical treatment outcomes: a meta-analysis. Med Care 2002;40:794–811.
62. Corrao G, Parodi A, Nicotra F, Zambon A, Merlino L, Cesana G, Mancia G. Better compliance to antihypertensive medications reduces cardiovascular risk. Journal of Hypertension 2011;29:610-618.
63. Mazzaglia G, Ambrosioni E, Alacqua M, Filippi A, Sessa E, Immordino V, et al. Adherence to Antihypertensive Medications and Cardiovascular Morbidity Among Newly Diagnosed Hypertensive Patients. Circulation 2009;120:1598-1605.
64. Dragomir A, Côté R, Roy L, Blais L, Lalonde L, Bérard A, Perreault S. Impact of Adherence to Antihypertensive Agents and Clinical Outcomes and Hospitalization Costs. Medical Care 2010;48(5)418-25.
65. Pittman D, Tao Z, Chen W, Stettin G. Antihypertensive Medication Adherence and Subsequent Healthcare Utilization and Costs. Am J Manag Care 2010;16(8):568-576.

66. Esposti ED, Sturani A, Di Martino M, Falasca P, Novi MV, Baio G, Buda S, Volpe M. Long-term persistence with antihypertensives drugs in new patients. J Hum Hypertens 2002;16:439-44.
67. Bugalho A, Carneiro AV. Intervenções para aumentar a adesão terapêutica em patologias crónicas. Norma de Orientação Clínica, ed. CEMBE da FML, 2004.
68. Caldeira D, Vaz-Carneiro A, Costa J. Impacto da frequência posológica na adesão terapêutica em doenças cardiovasculares crónicas: revisão sistemática e meta-análise. Rev Port Cardiol 2014;33:431-437.
69. Cramer JA. Patient outcomes. Consequences of Intermittent Treatment for Hypertension: The Case for Medication Compliance and Persistence. Am J Manag Care 1998;4:1563-68.
70. Simpson SH, Eurich DT, Majumdar SR, Padwal RS, Tsuyuki RT, Varney J, et al. A meta-analysis of the association between adherence to drug therapy and mortality. BMJ 2006;333:15.
71. Brookhart MA, Patrick AR, Dormuth C, Avorn J, Shrank W, Cadarette SM, et al. Adherence to lipid-lowering therapy and the use of preventive health services: an investigation of the healthy user effect. Am J Epidemiol 2007;166:348 –354.
72. Vrijens B, Urquhart J, White D. Electronically monitored dosing histories can be used to develop a medication-taking habit and manage patient adherence. Expert Rev Clin Pharmacol 2014 Sep;7(5):633-44
73. Cutler DM, Everett W. Thinking outside the pillbox–medication adherence as a priority for health care reform. N Engl J Med 2010;362:1553–1555.
74. Garfield S, Clifford S, Eliasson L, Barber N, Willson A. Suitability of measures of self-reported medication adherence for routine clinical use: a systematic review. BMC Med Res Methodol 2011;11:149.
75. Fischer MA, Vogeli C, Stedman MR, Ferris TG, Weissman JS. Uptake of Electronic Prescribing in Community-Based Practices. J Gen Intern Med 2007;23(4):358–63.
76. Boswell, KA, Cook, CL, Burch, SP, Eaddy, MT, Cantrell, CR. Associating Medication Adherence With Improved Outcomes: A Systematic Literature Review. Am J Pharm Benefits 2012;4(4):e97-e108.
77. Kardas P, ABC Project Team. Ascertaining Barriers for Compliance: policies for safe, effective and cost-effective use of medicines in Europe. Final Report of the ABC Project (Deliverable 7.1). 2002. Available from: http://abcproject.eu/img/ABC%20Final.pdf (06-05-2014).
78. Haynes RB, Montague P, Oliver T, et al. Interventions for helping patients to follow prescriptions for medications. Cochrane Database Syst Rev 2000(2):CD000011

79. Heidenreich PA. Patient adherence: the next frontier in quality improvement. Am J Med 2004;117:130 –132.
80. Marcum ZA, Sevick MA, Handler SM. Medication nonadherence: a diagnosable and treatable medical condition. JAMA 2013;309:2105–2106.
81. Sackett DL, Haynes RB. Compliance with Therapeutic Regimens. Baltimore, MD: The Johns Hopkins University Press, 1976.
82. Cabral MV, Silva PA. A adesão à terapêutica em Portugal: atitudes e comportamentos da população portuguesa perante as prescrições médicas. Imprensa de Ciências Sociais, 2010. ISBN 9789726712572.
83. van Wijk BLG, Klungel OH, Heerdink ER, de Boer A. The association between adherence with antihypertensive drugs and modification of antihypertensive drug regimen. J Hypertens 2004;22:1831-7.
84. Halpern MT, Khan ZM, Schmier JK, Burnier M, Caro JJ, Cramer J, Daley WL, Gurwitz J, Hollenberg NK. Recommendations for Evaluating Compliance and Persistence With Hypertension Therapy Using Retrospective Data. Hypertension 2006;47:1039-1048.
85. van Wijk BLG, Klungel OH, Heerdink ER, de Boer A. Refill persistence with chronic medication assessed from a pharmacy database was influenced by method of calculation. J Clin Epidemiol 2006;59:11-17.
86. van Wijk BLG, Klungel OH, Heerdink ER, de Boer A. Initial non-adherence with antihypertensive monotherapy is followed by complete discontinuation of antihypertensive therapy. Pharmacoepidemiol Drug Saf 2006;15:587-93.
87. Lowy A, Munk VC, Ong SH, Burnier M, Vrijens B, Tousset EP, Urquhart J. Effects on blood pressure and cardiovascular risk of variations in patients' adherence to prescribed antihypertensive drugs: role of duration of drug action. Int J Clin Pract 2011;65:41-53.
88. Hyre AD, Krousel-Wood MA, Muntner P, Kawasaki L, DeSalvo KB. Prevalence and predictors of poor antihypertensive medication adherence in an urban health clinic setting. J Clin Hypertens 2007;9:179-86.
89. Schroeder K, Fahey T, Ebrahim S. How can we improve adherence to blood pressure—lowering medication in ambulatory care? Arch Intern Med 2004;164:722-32.
90. Baggarly SA, Kemp RJ, Wang X, Magoun AD. Factors associated with medication adherence and persistence of treatment for hypertension in a Medicaid population. Res Social Adm Pharm. 2014 Nov-Dec;10(6):e99-112.
91. Bourgault C, Sénécal M, Brisson M, Marentette MA, Grégoire J-P. Persistence and discontinuation patterns of antihypertensives therapy among newly treated patients: a population-based study. J Hum Hypertens 2005;19:607-13.
92. Caro JJ, Salas M, Speckman JL, Raggio G, Jackson JD. Persistence with treatment for hypertension in actual practice. Can Med Assoc J 1999;160:31–37.

93. Grimmsmann T, Himmel W. Persistence of antihypertensive drug use in German primary care: a follow-up study based on pharmacy claims data. Eur J Clin Pharmacol 2014;70:295-301.
94. Hasford J, Schröder-Bernhardi D, Rottenkolber M, Kostev K, Dietlein G. Persistence with antihypertensive treatments: results of a 3-year follow-up cohort study. Eur J Clin Pharmacol 2007;63:1055–1061.
95. Burke TA, Sturkenboom MC, Lu SE, Wentworth CE, Lin Y, Rhoads GG. Discontinuation of antihypertensive drugs among newly diagnosed hypertensive patients in UK general practice. J Hypertens 2006;24:1193–1200
96. Cramer JA, Benedict Á, Muszbek N, Keskinaslan A, Khan ZM. The significance of compliance and persistence in the treatment of diabetes, hypertension and dyslipidaemia: a review. Int J Clin Pract 2008:62(1):76-87.
97. Burnier M, Wuerzner G, Struijker-Boudier H, Urquhart J. Measuring, Analyzing, and Managing Drug Adherence in Resistant Hypertension. Hypertension 2013;62:218-225.
98. Lowry KP, Dudley TK, Oddone EZ, Bosworth HB. Intentional and unintentional nonadherence to antihypertensive medication. Ann Pharmacother 2005;39:1198 –1203.
99. Gadkari AS, McHorney CA. Unintentional nonadherence to chronic prescription medications: how unintentional is it really? BMC Health Serv Res. 2012;12:98.
100. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. Circulation 2009;119(23):3028-35.
101. Raebel MA, Schmittdiel J, Karter AJ, Konieczny JL, Steiner JF. Standardizing Terminology and Definitions of Medication Adherence and Persistence in Research employing Electronic Databases. Med Care 2013;51(803):S11-S21.
102. Fischer MA, Stedman MR, Lii J, Vogeli C, Shrank W, Brookhart M, et al. Primary Medication Non-Adherence: Analysis of 195,930 Electronic Prescriptions. J Gen Intern Med 2010;25(4):284–90.
103. Shah NR, Hirsch AG, Zacker C, Wood GC, Schoenthaler A, Ogedegbe G, et al. Predictors of First-Fill Adherence for Patients With Hypertension. Am J Hypertens 2009 April;22(4):392–396.
104. Hutchins DS, Zeber JE, Roberts CS, Williams AF, Manias E, Peterson AM. Initial Medication Adherence—Review and Recommendations for Good Practices in Outcomes Research: An ISPOR Medication Adherence and Persistence Special Interest Group Report. Value Health 2015;18:690-699.
105. Arnet I, Kooij MJ, Messerli M, Hersberger KE, Heerdink ER, Bouvy M. Proposal of Standardization to Assess Adherence With Medication Records: Methodology Matters. Ann Pharmacother. 2016;50(5):360-8.

106. Singer SR, Hoshen M, Shadmi E, Leibowitz M, Flaks-Manov N, Bitterman H, Balicer RD. EMR-Based Medication Adherence Metric Markedly Enhances Identification of Nonadherent Patients. Am J Manag Care 2012;18(10):e372-e377.
107. Shrank W, Choudhry N, Fischer M, Avorn J, Powell M, Schneeweiss S, et al. The Epidemiology of Prescriptions Abandoned at the Pharmacy. Ann Intern Med 2010;153:633-640.
108. Karter AJ, Parker MM, Moffet HH, Ahmed AT, Schmittdiel JA, Selby JV. New prescription medication gaps: A comprehensive measure of adherence to new prescriptions. Health Serv Res 2009; 44:1640–1661.
109. Raebel MA, Carroll NM, Ellis JL, Schroeder EB, Bayliss EA. Importance of Including Early Nonadherence in Estimations of Medication Adherence. Ann Pharmacother 2011;45:1053-60.
110. Fischer MA, Choudhry NK, Brill G, Avorn J, Schneeweiss S, Hutchins D, et al. Trouble Getting Started: Predictors of Primary Medication Nonadherence. Am J Med 2011;124(11):1081.e9-1081.e22.
111. Tamblyn R, Eguale T, Huang A, Winslade N, Doran P. The Incidence and Determinants of Primary Nonadherence With Prescribed Medication in Primary Care. Ann Intern Med 2014;160:441-50.
112. Cooke C, Xing S, Lee H, Belletti D. You wrote the prescription, but will it get filled? J Fam Pract 2011;60(6):321-327.
113. Raebel MA, Ellis J, Carroll NM, Bayliss EA, McGinnis B, Schroeder EB, et al. Characteristics of Patients with Primary Non-adherence to Medications for Hypertension, Diabetes, and Lipid Disorders. J Gen Intern Med 2011.
114. Ebrahim S. Detection, adherence and control of hypertension for the prevention of stroke: a systematic review. Health Technol Assess 1998;2:1-78.
115. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. BMJ 2008;336(7653):1114-7.
116. Urquhart J, Vrijens B. New findings about patient adherence to prescribed drug dosing regimens: an introduction to pharmionics. Eur J Hosp Pharm Science 2005;11:103-6.
117. Urquhart J. The electronic medication event monitor: lessons for pharmacotherapy. Clin Pharmacokinet 1997;32:345-56.
118. Urquhart J. The odds of the three nons when an aptly prescribed medicine isn't working: non-compliance, non-absorption, non-response. Br J Clin Pharmacol 2002;54:212-20.
119. Feinstein AR. On white-coat effects and the electronic monitoring of compliance. Arch Intern Med 1990;150:1509-10.

120. Cramer JA, Scheyer RD, Mattson RH. Compliance declines between clinic visits. Arch Intern Med 1990;150:1377-8.
121. Qvarnström M, Kahan T, Kieler H, Brandt L, Hasselström J, Boström KB, et al. Persistence to antihypertensive drug treatment in Swedish primary healthcare. Eur J Clin Pharmacol 2013;69:1955–1964.
122. Vrijens B, Heidbuchel H. Non-vitamin K antagonist oral anticoagulants: considerations on once- vs. twice-daily regimens and their potential impact on medication adherence. Europace 2015;17:514–523.
123. Frishman WH. Importance of medication adherence in cardiovascular disease and the value of once-daily treatment regimens. Cardiol Rev 2007;15(5):257-63.
124. Morgan SG, Yan L: Persistence with hypertension treatment among community-dwelling BC seniors. Can J Clin Pharmacol 2004;12: e267–e273.
125. Burnier M, Santschi V, Favrat B, Brunner HR. Monitoring compliance in resistant hypertension: an important step in patient management. J Hypertens 2003;21(Suppl 2):S37–S42.
126. Heisler M, Hogan MM, Hofer TP, et al. When more is not better: treatment intensification among hypertensive patients with poor medication adherence. Circulation 2008;117:2884–92.
127. Krousel-Wood M, Thomas S, Muntner P, Morisky D. Medication adherence: a key factor in achieving blood pressure control and good clinical outcomes in hypertensive patients. Curr Opin Cardiol 2004;19:357–362.
128. Kardas P, Lewek P, Matyjaszczyk M. Determinants of patient adherence: a review of systematic reviews. Front Pharmacol 2013;4:91
129. Scheurer, D, Choudhry, N, Swanton, KA, Matlin, O, Shrank, W. Association Between Different Types of Social Support and Medication Adherence. Am J Manag Care 2012;18(12):e461-e467.
130. Vermeire, E, Hearnshaw, H, Van Royen, P, Denekens, J. Patient adherence to treatment: three decades of research. A comprehensive review. J Clin Pharm Ther 2001;26:331-42
131. Briesacher BA, Andrade SE, Fouayzi H, Chan KA. Medication Adherence and Use of Generic Drug Therapies. Am J Manag Care 2009;15(7):450-456.
132. Choudhry N, Avorn J, Glynn R, Antman E, Schneeweiss S, Toscano M, et al. Full Coverage for Preventive Medications after Myocardial Infarction. N Engl J Med 2011; 365:2088-2097.
133. Corrao G, Soranna D, La Vecchia C, Catapano A, Agabiti-Rosei E, Gensini G, et al. Medication persistence and the use of generic and brand-name blood pressure-lowering agents. J Hypertens 2014;32:1146-1153.

134. Observatório Português dos Sistemas de Saúde. Relatório de Primavera 2013. Duas faces da saúde. OPSS, 2013.
135. Celentano A, Palmieri V, Arezzi E, Sabatella M, Guillaro B, Brancati C, et al. Cardiovascular secondary prevention: patients' knowledge of cardiovascular risk factors and their attitude to reduce the risk burden, and the practice of family doctors. The "Help Your Heart Stay Young" study. Ital Heart J 2004;5:767–773.
136. Dunbar-Jacob J, Mortimer-Stephens MK. Treatment adherence in chronic disease. J Clin Epidemiol 2001;54:S57-S60.
137. Garner JB. Problems of nonadherence in cardiology and proposals to improve outcomes. Am J Cardiol 2010;105(10):1495-1501.
138. van Dulmen S, Sluijs E, van Dijk L, de Ridder D, Heerdink R, Bensing J. Patient adherence to medical treatment: a review of reviews. BMC Health Serv. Res. 2007;7:55.
139. Benner JS, Chapman RH, Petrilla AA, Tang SSK, Rosenberg N, Schwartz JS. Association between prescription burden and medication adherence in patients initiating antihypertensive and lipid-lowering therapy. Am J Health-Syst Pharm 2009;66:1471-7.
140. Bae, JP, Dobesh, PP, Klepser, DG, et al. Adherence and Dosing Frequency of Common Medications for Cardiovascular Patients. Am J Manag Care 2012;18(3):139-46.
141. Daugherty SL, Powers JD, Magid DJ, Masoudi FA, Margolis KL, O'Connor PJ, et al. The Association Between Medication Adherence and Treatment Intensification With Blood Pressure Control in Resistant Hypertension. Hypertension 2012;60:303-309.
142. Iskedjian M, Einarson TR, MacKeigan LD, Shear N, Addis A, Mittmann N, et al. Relationship between daily dose frequency and adherence to antihypertensive pharmacotherapy: evidence from a meta-analysis. Clin Therap 2002;24:302-316.
143. Moise N, Schwartz J, Bring R, Shimbo D, Kronish IM. Antihypertensive Drug Class and Adherence: An Electronic Monitoring Study. Am J Hypertens 2015 Jun;28(6):717-21.
144. McDonald, HP, Garg, AX, Haynes, RB. Interventions to Enhance Patient Adherence to Medication Prescriptions: Scientific Review. JAMA 2002;288(22):2868-2879.
145. Zeng F, Patel BV, Andrews L, Frech-Tamas F, Rudolph AE. Adherence and persistence of single-pill ARB/CCB combination therapy compared to multiple-pill ARB/CCB regimens. Curr Med Res Opin 2010;26:2877–2887.
146. DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. Med. Care 2004;42:200–209.
147. Demonceau J, Ruppar T, Kristanto P, et al. Identification and assessment of adherence-enhancing interventions in studies assessing medication adherence through

electronically compiled drug dosing histories: a systematic literature review and meta-analysis. Drugs 2013;73(6):545-62

148. Hill MN, Miller NH, DeGeest S, on Behalf of the American Society of Hypertension. ASH Position Paper: Adherence and Persistence With Taking Medication to Control High Blood Pressure. J Clin Hypertens. 2010;12:757–764.
149. Maia C. Aderência à terapêutica. Aspectos práticos em Medicina Familiar. Revista Factores de Risco 2008;11:42-45.
150. Krousel-Wood M, Muntner P, Islam T, Morisky DE, Webber LS. Barriers to and Determinants of Medication Adherence in Hypertension Management: Perspective of the Cohort Study of Medication Adherence among Older Adults (CoSMO). Med Clin North Am 2009;93(3):753-769.
151. Borzecki AM, Oliveria SA, Berlowitz DR. Barriers to hypertension control. Am Heart J 2005;149:785-794.
152. Barat I, Andreasen F, Damsgaard, EMS. Drug therapy in the elderly: what doctors believe and patients actually do. Br J Clin Pharmacol 2001;51:615-622.
153. Wang, PS, Benner, JS, Glynn, RJ, Winkelmayer, WC, Mogun, H, Avorn, J. How well do patients report noncompliance with antihypertensive medications?: a comparison of self-report versus filled prescriptions. Pharmacoepidemiol Drug Saf 2004;13:11–19.
154. Morrison A, Wertheimer AI, Berger ML. Interventions to improve antihypertensive drug adherence: a quantitative review of trials. Formulary 2000;35:234-55.
155. Hamdidouche I, Jullien V, Billaud EM, Boutouyrie P, Azizi M, Laurent S. Routine urinary detection of antihypertensive drugs for estimation of adherence to treatment: a cross sectional study. J Hypertens 2015 Jun;33 Suppl 1:e93.
156. Noize P, Bazin F, Dufouil C, Lechevallier-Michel N, Ancelin ML, Dartigues JF, et al. Comparison of health insurance claims and patient interviews in assessing drug use: data from the Three-City (3C) Study. Pharmacoepidemiol Drug Saf 2009;18:310–319. doi: 10.1002/pds.1717
157. Hall GC, Sauer B, Bourke A, Brown JS, Reynolds MW, Casale RL. Guidelines for Good Database Selection and use in Pharmacoepidemiology Research. Pharmacoepidemiol Drug Saf 2012;21:1-10. doi: 10.1002/pds
158. Grimmsmann T, Himmel W. Discrepancies between prescribed and defined daily doses: a matter of patients or drug classes? Eur J Clin Pharmacol 2011;67(8):847–54.
159. Rikala M, Hartikainen S, Saastamoinen LK, Korhonen MJ. Measuring psychotropic drug exposures in register-based studies – validity of a dosage assumption of one unit per day in older Finns. Int. J. Methods Psychiatr. Res. 2013;22(2):155–165

160. Hess LM, Raebel MA, Conner DA, et al. Measurement of adherence in pharmacy administrative databases: A proposal for standard definitions and preferred measures. Ann Pharmacother. 2006;40:1280–1288.
161. Hansen RA, Kim MM, Song L, et al. Comparison of methods to assess medication adherence and classify nonadherence. Ann Pharmacother 2009; 43:413–422.
162. Vink NM, Klungel OH, Stolk RP, Denig P. Comparison of various measures for assessing medication refill adherence using prescription data. Pharmacoepidemiol Drug Saf 2009;18(2):159-65.
163. Caetano PA, Lam JM, Morgan SG. Toward a standard definition and measurement of persistence with drug therapy: Examples from research on statin and antihypertensive utilization. Clin Ther 2006;28:1411-1424.
164. Administração Regional de Saúde de Lisboa e Vale do Tejo. Perfil de Saúde e Seus Determinantes da Região de Lisboa e Vale do Tejo, Volume 1. 2015. Available from: http://www.arslvt.min-saude.pt/uploads/writer_file/document/875/VOL1_-_Perfil_de_Sa_de_-_Determinantes.pdf
165. Barros P, Machado S, Simões J. Portugal: Health system review. Health Syst Transit. 2011;13(4):1–156.
166. INFARMED. Estatística do Medicamento 2011. Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MONITORIZACAO_DO_MERCADO/OBSERVATORIO/ESTATISTICA_DO_MEDICAMENTO/EstMed-2011.pdf
167. Portugal, Ministry of Health: Decreto-Lei n.º 106-A/2010, de 1 de Outubro.
168. Portugal, Ministry of Health: Monitorização da Prescrição de Medicamentos de Ambulatório e Meios Complementares de Diagnóstico e Terapêutica. Indicadores Nacionais e Locais (Fevereiro 2011 a Junho 2012). Available from: http://www.min-saude.pt/NR/rdonlyres/7CF854E1-5956-4C19-9FC2-276C17B31A3C/0/relatorio_mpm_fev11_jun12__final.pdf
169. Portugal, Ministry of Health: Portaria n.º 137-A/2012, de 11 de Maio.
170. Administração Central do Sistema de Saúde, IP. Manual de Relacionamento das Farmácias com o Centro de Conferência de Faturas do SNS. Outubro de 2015. Available from: https://www.ccf.min-saude.pt/portal/page/portal/estrutura/documentacaoPublica/ACSS/Manual%20de%20Relacionamento%20de%20Farm%C3%A1cias_v1.17.pdf
171. Portugal, Ministry of Health: Portaria n.º 195-D/2015, de 15 de Junho.
172. Administração Central dos Serviços de Saúde. Classificação Internacional de Cuidados de Saúde Primários: 2ª edição. 2011. Available from: http://www.acss.min-saude.pt/Portals/0/apmcg_ICPC%20v%201.7.pdf

173. Coelho A, Vilares C, Caetano PA. Adequabilidade de uma posologia padrão diária à prática clínica para 163 medicamentos anti-hipertensivos usados no tratamento da hipertensão arterial. Revista Portuguesa de Hipertensão e Risco Cardiovascular. Forthcoming 2016.
174. Ax F, Ekedahl A. Electronically transmitted prescriptions not picked up at pharmacies in Sweden. Res Social Adm Pharm 2010;6:70–77.
175. Bohm M, Baumhakel M, Mahfoud F, Werner C. From evidence to rationale: cardiovascular protection from angiotensin II receptor blockers compared with angiotensin-converting enzyme inhibitors. Cardiology 2010;117(3):163-173.
176. Kettani FZ, Dragomir A, Côté R, Roy L, Bérard A, Blais L, et al. Impact of a better adherence to antihypertensive agents on cerebrovascular disease for primary prevention. Stroke 2009;40:213-20.
177. Psaty BM, Koepsell TD, Wagner EH, LoGerfo JP, Inui TS. The relative risk of incident coronary heart disease associated with recently stopping the use of beta-blockers. JAMA 1990;263(12):1653-7.
178. Girvin BG, Johnston GD. Comparison of the effects of a 7-day period of non-compliance on blood pressure control using three different antihypertensive agents. J Hypertens 2004;22(7):1409-14.
179. Haynes RB, Dantes R. Patient compliance in the design and interpretation of clinical trials. Control Clin Trials 1987;8(1):12-19.
180. Coelho A, Rodrigues C, Vilares C, Silva M, Costa M, Caetano PA, et al. Investigação sobre adesão à terapêutica na população portuguesa – uma revisão de âmbito. Revista Portuguesa de Medicina Geral e Familiar. Forthcoming 2016.
181. Morenoff JD, House JS, Hansen BB, Williams DR, Kaplan GA, Hunte HE. Understanding social disparities in hypertension prevalence, awareness, treatment, and control: the role of neighborhood context. Soc Sci Med 2007;65:1853–1866.
182. van Wijk BLG, Klungel OH, Heerdink ER, de Boer A. Generic substitution of antihypertensive drugs: Does it affect adherence? Ann Pharmacother. 2006;40(1):15-20.
183. Ordem dos Farmacêuticos. Boas Práticas Farmacêuticas para a farmácia comunitária (BPF2009). 2009. Available from: http://www.ordemfarmaceuticos.pt/xFiles/scContentDeployer_pt/docs/Doc3082.pdf
184. Mabotuwana T, Warren J, Harrison J, Kenealy T. What can primary care prescribing data tell us about individual adherence to long-term medication?—comparison to pharmacy dispensing data. Pharmacoepidemiol Drug Saf 2009;18: 956–964.

SUMÁRIO

INTRODUÇÃO

As doenças cardiovasculares (DCV) são, em Portugal, a principal causa de morte, sendo responsáveis por 32% do total dos óbitos no País. A hipertensão arterial (HTA) é uma doença crónica de elevada prevalência e um fator de risco *major* para as DCV contribuindo, quando não tratada, para a redução da esperança média de vida em aproximadamente 5 anos.

Os benefícios da terapêutica anti-hipertensiva (TAH) têm sido extensamente demonstrados, através da associação comprovada entre a redução da pressão arterial e a redução das complicações cardiovasculares, como sejam enfarte, doença isquémica, insuficiência cardíaca ou doença renal.

Não obstante, e apesar da crescente disponibilização no mercado de novos medicamentos, com efetividade e tolerância demonstradas, o controlo da HTA permanece a níveis inadequados. Em Portugal, estima-se que apenas 42.5% dos doentes hipertensos tenham a sua pressão arterial controlada (inferior a 140/90 mmHg).

Diferentes fatores contribuirão para esta realidade, no entanto, um grande (e modificável) fator prende-se com o facto de que muitas vezes os doentes não só não tomam a medicação como lhes foi prescrita/recomendada (não-adesão) como não a tomam de forma contínua/ininterrupta durante longos períodos de tempo (não-persistência), interrompendo periodicamente ou de forma definitiva o tratamento.

No caso particular da HTA, uma inadequada adesão à TAH e/ou a falha na persistência no tratamento contribuem para o desenvolvimento das complicações cardiovasculares representando, assim, uma parte importante da mortalidade e morbilidade cardiovascular que poderia ser prevenida, tendo um impacto significativo nos *outcomes* clínicos do tratamento da HTA, nas hospitalizações e nos custos associados aos cuidados de saúde prestados a estes doentes.

De uma forma geral, a adesão à terapêutica refere-se ao processo pelo qual os doentes tomam os medicamentos de acordo com uma dada prescrição/recomendação médica,

integrando três componentes distintas entre si: iniciação, implementação e descontinuação.

O processo começa com a iniciação do tratamento, quando o doente toma a primeira dose do medicamento prescrito. A partir desse ponto ocorre a implementação do tratamento, sendo que nesta etapa o doente toma a medicação tendo em conta uma determinada posologia prescrita até à última dose. A descontinuação marca o fim do tratamento, não sendo tomadas mais doses posteriormente. O período de tempo entre a iniciação e a descontinuação denomina-se persistência.

Deste modo, a não-adesão à terapêutica pode ocorrer numa (ou em mais do que uma) das seguintes situações: atraso ou não-iniciação do tratamento, má implementação ou interrupção precoce do tratamento prescrito.

A adesão à terapêutica é habitualmente expressa como uma fração ou percentagem das doses prescritas e que foram realmente tomadas pelo doente durante um período específico de tempo.

A literatura descreve diversos métodos para a realização de estudos de adesão à terapêutica, incluindo (i) questionários dirigidos aos doentes / autorrelatos dos doentes; (ii) contagem de comprimidos; (iii) utilização de monitores eletrónicos de medicação; (iv) utilização de marcadores bioquímicos; (v) taxas de renovação de prescrições, entre outros.

A taxa de renovação de prescrições, através da consulta de bases de dados de prescrições médicas e/ou de dispensa/faturação das farmácias comunitárias permite o estudo da adesão à terapêutica em grandes populações, nas suas três componentes - iniciação, implementação e descontinuação - sendo inclusivamente considerado o método *gold standard* para o estudo das componentes de iniciação (nos casos em que é possível interligar os registos de prescrição com os registos de faturação) e descontinuação (embora a análise seja sempre retrospetiva).

Quando se recorre a bases de dados para o estudo da adesão à terapêutica, particularmente no que diz respeito à avaliação da componente da implementação,

várias medidas são descritas na literatura, entre as quais o *medication possession ratio* (MPR) e a *proportion of days covered* (PDC). Com algumas diferenças entre si, ambas representam medidas de disponibilidade da medicação prescrita/dispensada durante um intervalo de tempo específico. Habitualmente são calculadas dividindo o número de dias para os quais a medicação foi prescrita/dispensada durante um determinado período de tempo, pelo número de dias que decorreram desde a primeira dispensa até ao final desse período.

Já no caso da persistência no tratamento, esta é habitualmente expressa pela definição de um período de tempo máximo, para o qual se aceita que o doente esteja sem medicação.

Na literatura, a investigação sobre adesão à terapêutica é realizada predominantemente com doentes já em tratamento, avaliando a execução/implementação do mesmo. No entanto, observam-se valores mais baixos de adesão quando se avaliam novos doentes e se consideram não só a implementação do tratamento, como a sua (não) iniciação, uma eventual descontinuação precoce do tratamento ou simplesmente a descontinuação completa do tratamento ao final de um determinado período de tempo.

Que seja do nosso conhecimento, este é o primeiro estudo de base populacional em Portugal que avalia a adesão à terapêutica nas suas três componentes (principalmente relevante nas componentes da iniciação e descontinuação), através do recurso a bases de dados de prescrições médicas e dispensa/faturação em farmácias comunitárias.

OBJETIVO

Esta tese tem como objetivo geral determinar a adesão à terapêutica anti-hipertensiva, nas suas três componentes – iniciação, implementação e descontinuação – em doentes que iniciem tratamento da hipertensão arterial nas unidades de cuidados de saúde primários da Região de Saúde de Lisboa e Vale do Tejo. Adicionalmente, pretende-se identificar fatores de risco para a não-adesão, em cada uma das componentes do processo de adesão à terapêutica.

MATERIAIS E MÉTODOS

Esta tese corresponde a um estudo observacional, especificamente, um estudo de coorte retrospetivo. A coorte foi constituída por todos os doentes com registo de diagnóstico de HTA (códigos k86 e k87 da classificação ICPC-2) nas unidades de cuidados de saúde primários da região de saúde de Lisboa e Vale do Tejo e a quem, em consequência desse diagnóstico, foi prescrita TAH (independentemente do número de medicamentos anti-hipertensivos) durante o primeiro trimestre de 2011.

Os medicamentos anti-hipertensivos considerados foram todos aqueles que das seguintes categorias (de acordo com a classificação ATC) apresentam explicitamente no seu Resumo das Características do Medicamento "hipertensão" como indicação terapêutica: C02 – Anti-hipertensores; C03 – Diuréticos; C07 – Agentes betabloqueadores; C08 – Bloqueadores dos canais de cálcio e C09 – Agentes que atuam no sistema renina-angiotensina.

Os registos de prescrição e de faturação (dispensa mediante a apresentação de uma receita médica) foram recolhidos para cada doente, referentes a um período de dois anos após a data da primeira aquisição de pelo menos um anti-hipertensivo numa farmácia comunitária.

Para uma correta identificação dos *novos* utilizadores de TAH, para cada elemento da coorte foram ainda recolhidos os registos de prescrição e faturação para um período de seis meses prévios a 1 de janeiro de 2011 (período de *run-in*). Deste modo, todos os doentes com pelo menos um registo de prescrição e/ou faturação de medicamentos anti-hipertensivos durante este período foram classificados como utilizadores habituais de TAH (por oposição aos *novos* utilizadores) e dessa forma foram excluído da coorte.

Para além da avaliação das três componentes do processo de adesão à terapêutica, avaliamos ainda a adesão primária à TAH, expressa pela relação entre o número de registos de faturação sobre o número de registos de prescrição, medida em proporção. Nesta análise, a ausência de um registo de faturação para um registo de prescrição de um medicamento anti-hipertensivo foi considerada como não-adesão primária.

A iniciação da TAH foi definida pela proporção de doentes que adquiriu o primeiro medicamento anti-hipertensivo prescrito nos seis meses após a data da primeira prescrição. O intervalo de dias entre a primeira prescrição e a primeira aquisição foi definido como tempo para iniciação.

A implementação do regime terapêutico prescrito foi avaliada através da determinação do MPR, correspondendo este à relação entre o total de dias para os quais foi dispensada medicação e o total de dias em estudo (dois anos):

$$MPR = \frac{\text{n.º total de dias para os quais foi dispensada medicação}}{\text{n.º total de dias em estudo}} \text{ x } 100$$

Nos casos em que se verificaram alterações ao regime terapêutico inicial, com a adição e/ou a substituição dos medicamentos inicialmente prescritos/dispensados, o denominador do MPR foi ajustado. Para os utilizadores de múltiplos medicamentos anti-hipertensivos durante o período em estudo, foi determinado o MPR para cada medicamento individualmente, correspondendo o MPR por doente, à média dos MPR por cada medicamento utilizado por esse doente.

Em função do MPR determinado, os doentes foram inicialmente categorizados em três níveis de implementação: baixa (< 40%), intermédia (40-79%) e alta (≥ 80%). Numa fase seguinte foram categorizados de forma dicotómica, com base no ponto de corte de 80%.

A persistência no tratamento corresponde ao intervalo de tempo entre a primeira aquisição de um medicamento anti-hipertensivo e o final da embalagem do último medicamento adquirido. Para cada um dos elementos da coorte, todos os registos de faturação foram analisados consecutivamente e um intervalo de tempo igual ou superior a 90 dias entre a duração do último medicamento dispensado e a aquisição do seguinte, foi considerado como episódio de descontinuação do tratamento, sendo a data do final do último medicamento dispensado definida como a data de descontinuação. Não se observando descontinuação do tratamento durante os dois anos do período de observação, os doentes foram classificados como persistentes.

A reiniciação do tratamento foi também analisada e nesse sentido, apenas foi considerada a data do final do último medicamento dispensado, como data de descontinuação, independentemente da existência de um ou mais episódios de descontinuação durante o período de observação.

Para a análise da implementação e da persistência no tratamento, o número de dias para os quais foi dispensada medicação foi definido através de uma posologia padrão diária cuja aplicabilidade à prática clínica foi avaliada com recurso a um painel de 30 clínicos.

De forma a identificar os fatores de risco para as várias componentes da adesão à terapêutica, recorreu-se à análise de sobrevivência e a modelos de regressão de Cox para estimar os *hazard ratio* (HR) para a iniciação e a descontinuação da TAH e ao um modelo de regressão logística para estimar os *odds ratio* (OR) para níveis baixos de implementação do regime terapêutico prescrito.

RESULTADOS

Durante o primeiro trimestre de 2011, 29,896 doentes foram diagnosticados com hipertensão (códigos k86 e k87, classificação ICPC-2) nas unidades de cuidados de saúde primários da Região de Saúde de Lisboa e Vale do Tejo. Após a aplicação dos critérios de exclusão, constitui-se uma coorte com 10,204 doentes, 4,645 homens e 5,559 mulheres com idades compreendidas entre os 18 e os 90 anos, com uma idade média de 61.0±13.0 anos e uma mediana de 61.0 anos.

Aproximadamente ¾ (73.9%) dos elementos da coorte residiam na Área Metropolitana de Lisboa (AML) no primeiro trimestre de 2011; com base nos códigos das freguesias de residência foi possível determinar o poder de compra para cada elemento da coorte, tendo-se verificado que cerca de um em cada três elementos residia em municípios com baixo poder de compra.

A larga maioria (93.3%) dos doentes foi diagnosticada com ‘hipertensão sem complicações’ – código k86 – apesar de diferenças entre o género e a idade dos doentes:

a proporção de doentes diagnosticados com ‘hipertensão com complicações’ foi superior nos homens e em doentes com idade igual ou superior a 65 anos.

De uma forma geral, das 182,841 embalagens de medicamentos anti-hipertensivos prescritas durante o período de observação, 107,024 foram dispensadas numa farmácia comunitária, o que corresponde a uma taxa de adesão primária de 58.5%. A adesão primária aumentou com a idade dos doentes ($p<0.001$), foi maior nos homens ($p=0.020$), nos doentes residentes na AML ($p<0.001$) e para os doentes diagnosticados com hipertensão sem complicações ($p=0.001$).

Não se verificaram diferenças na taxa de adesão primária para os medicamentos genéricos comparativamente aos medicamentos de marca ($p=0.710$), nem quando o medicamento foi prescrito pelo médico de família do doente ou por outro especialista em medicina geral e familiar (58.9% *vs* 58.1%; $p=0.117$).

Analisando a adesão primária em função da classe farmacológica, verificamos que os agentes que atuam no sistema renina-angiotensina (C09), particularmente os inibidores da enzima de conversão da angiotensina (IECAs) e os antagonistas dos recetores da angiotensina II (ARAs) apresentaram as taxas mais elevadas, especialmente para as associações fixas (60.2% *vs* 59.1% para os ARAs e 59.1% *vs* 57.8% para os IECAs). Aumentando o custo para o doente, verificou-se uma diminuição da adesão primária, mais relevante para os diuréticos e os betabloqueadores e menos relevante para os agentes que atuam no sistema renina-angiotensina.

Do total dos 10,204 elementos da coorte, 493 (4.8%) não adquiriram qualquer medicamento anti-hipertensivo durante o período de observação e adicionalmente, 855 (8.4%) apesar de iniciarem tratamento, fizeram-no com um atraso considerável relativamente à data da primeira prescrição (507.2±182.6 dias). Portanto, a taxa de iniciação traduziu-se em 86.8%, aumentando com a idade ($p<0.001$) e diminuindo com o poder de compra ($p=0.007$).

O tempo para iniciação foi inferior nos homens comparativamente às mulheres (25.8±27.3 *vs* 27.0±28.2 dias), aumentando a diferença com o passar do tempo

(p=0.024) e para doentes mais jovens (idade inferior a 45 anos) comparativamente com os doentes mais velhos (p=0.030).

Tal como para a adesão primária, o facto do(s) primeiro(s) medicamento(s) ter(em) sido prescrito(s) pelo médico de família do doente ou por outro clínico, não influenciou a decisão de iniciar o tratamento da hipertensão.

Doentes para os quais foram inicialmente prescritos dois ou mais medicamentos (sejam em separado ou em associações fixas), apresentaram uma maior taxa de iniciação, diminuindo esta, no entanto, com os custos imputados ao doente (88.2% para custos <5€ *vs* 83.6% para custos ≥10€; p<0.001), não se verificando diferenças entre medicamentos genéricos e medicamentos de marca (86.1% *vs* 85.6%; p=0.497).

Tal como para a adesão primária, doentes aos quais foram prescritos IECAs ou ARAs (C09) apresentaram as taxas de iniciação mais elevadas, especialmente para as associações fixas no caso dos IECAs (87.2% *vs* 86.0%).

Após ajustamento aos vários potenciais preditores para a iniciação, o modelo de regressão de Cox demonstrou que a idade, o género e o medicamento inicialmente prescrito (em termos do número de medicamentos prescritos e da classe farmacológica) relacionam-se com a iniciação da TAH.

Entre os docentes com uma primeira dispensa de um medicamento anti-hipertensivo (n=8,856), 303 (7.5%) homens e 335 (7.0%) mulheres descontinuaram completamente o tratamento após a primeira dispensa (embora sem diferenças estatisticamente significativas entre os géneros), não adquirindo mais nenhum medicamento durante o período de observação, i.e. descontinuação precoce.

A descontinuação precoce foi mais comum nos doentes mais jovens (abaixo dos 45 anos: 19.7% *vs* 4.0% nos doentes com idade igual ou superior a 65 anos; p<0.001), nos doentes diagnosticados com hipertensão sem complicações (7.2% *vs* 3.7% para os doentes diagnosticados com hipertensão com complicações; p=0.003) e nos residentes na região do Médio Tejo. Não se verificou associação entre o poder de compra e a descontinuação precoce da TAH.

Analisando o efeito da classe farmacológica utilizada inicialmente na decisão de descontinuar de forma prematura o tratamento, os nossos dados indicam que os doentes que iniciaram o tratamento com um betabloqueador ou um diurético apresentaram uma maior taxa de descontinuação precoce do que os doentes que iniciaram tratamento com um IECA ou um ARA. Estas diferenças foram estatisticamente significativas ($p<0.001$).

Também à semelhança das análises anteriores, o uso de associações fixas, bem como o custo por embalagem inferior a 5€ tiveram impacto positivo na decisão de prolongar o tratamento pelo menos para além da primeira embalagem prescrita/adquirida. Não se verificaram diferenças estatisticamente significativas entre os doentes que iniciaram tratamento com um medicamento genérico comparativamente aos que iniciaram tratamento com um medicamento de marca (8.7% *vs* 8.4%; $p=0.569$).

Durante o primeiro ano de tratamento, 21.6% dos homens e 23.1% das mulheres não tiveram qualquer episódio de descontinuação da TAH, reduzindo, no entanto, esses valores para 5.8% nos homens e 6.3% nas mulheres, no final do segundo ano de tratamento. As diferenças entre os géneros foram estatisticamente significativas ($p=0.037$), apresentando as mulheres uma maior persistência.

A persistência diminuiu de forma clara com a idade: apenas 1.8% (16) dos doentes com idade inferior a 45 anos não teve qualquer episódio de descontinuação do tratamento *vs* 8.2% dos doentes com idade igual ou superior a 65 anos. A persistência também se revelou menor no escalão mais elevado do poder de compra (4.4% *vs* 6.0%; $p=0.034$) e para os doentes diagnosticados com hipertensão sem complicações (5.8% *vs* 9.4%; $p=0.001$).

Doentes que iniciaram tratamento com um diurético em formulação simples apresentaram a menor persistência (3.8%) para todas as classes farmacológicas, ao passo que o valor mais elevado se verificou para os doentes que iniciaram tratamento com uma associação fixa de dois diuréticos (7.7%). No entanto, é importante referir que esta análise apenas teve em consideração o(s) medicamento(s) utilizado(s) no início do tratamento, independentemente do(s) mesmo(s) ser(em) substituído(s)/complementado(s) durante o período de observação.

Após ajustamento aos vários potenciais preditores para a descontinuação (não-persistência), o modelo de regressão de Cox demonstrou que a idade, o número de medicamentos dispensados por doente durante o período de observação e o número de prescritores para o mesmo doente relacionam-se com a descontinuação da TAH.

Quando se tem em consideração a reiniciação do tratamento e se ajusta a definição de persistência em função dessa reiniciação, a persistência aumenta consideravelmente, verificando-se que a larga maioria dos doentes reiniciam o tratamento após um episódio de descontinuação durante o período de observação e dessa forma, no final do segundo ano, 72.2% ainda se encontram em tratamento com pelo menos um medicamento anti-hipertensivo, com uma maior proporção de mulheres (73.6% *vs* 70.6%; p=0.002) e de doentes com idade igual ou superior a 65 anos (79.4% *vs* 48.5% de doentes com igual inferior a 45 anos).

Os doentes residentes no Médio Tejo apresentaram uma maior descontinuação (mesmo tendo em consideração uma possível reiniciação do tratamento), tal como os doentes diagnosticados com hipertensão sem complicações (26.2% *vs* 21.1%; p=0.012).

Analisando a persistência (incluindo a reiniciação) em função da classe farmacológica, verifica-se que doentes que iniciaram tratamento com um diurético (isolado ou em associação fixa) ou um betabloqueador apresentarem menor persistência. Doentes que iniciaram tratamento com uma associação fixa de um ARA ou um IECA com um BEC ou um diurético apresentaram maior persistência comparativamente às formulações isoladas desses medicamentos (73.0% *vs* 69.7% para os IECAs e 73.3% *vs* 72.0% para os ARAs).

Após ajustamento aos vários potenciais preditores para a descontinuação, não considerando períodos os episódios de descontinuação, o modelo de regressão de Cox demonstrou que a idade, o número de medicamentos dispensados por doente durante o período de observação, o número de prescritores para o mesmo doente, o poder de compra e a classe farmacológica inicialmente prescrita relacionam-se com a descontinuação da TAH.

Por fim, analisando a implementação do tratamento ao longo dos dois anos de observação, apenas 456 (5.1%) doentes tiveram medicação disponível para 80% ou mais dos dias de tratamento, principalmente os homens (5.4% *vs* 4.9% das mulheres), embora esta diferença não tenha sido estatisticamente significativa. Em média, os doentes tiveram medicação para 43.6±23.1% (em dias) dos dois anos do período de observação (mediana: 44.0%).

Níveis mais elevados de implementação foram também encontrados nos doentes com idade igual ou superior a 65 anos, e para as restantes variáveis de caracterização dos doentes não se encontraram quaisquer diferenças com significado estatístico. No entanto, verificou-se uma tendência para níveis mais elevados de implementação nos doentes com menor poder de compra.

Tal como nas análises anteriores, também na implementação do regime terapêutico, os níveis mais baixos foram encontrados para os diuréticos (42.3% nas associações fixas) e os níveis mais elevados para as associações fixas de IECAs e ARAs com outros anti-hipertensivos.

O modelo de regressão logística demonstrou que a idade, o número de medicamentos dispensados por doente durante o período de observação, o número de prescritores para o mesmo doente, e o poder de compra relacionam-se com níveis mais baixos de implementação da TAH. No entanto, e contrariamente ao que se verificou para a persistência, um maior número de medicamentos dispensados por doente diminui a qualidade da implementação.

DISCUSSÃO E CONCLUSÕES

Os resultados desta tese confirmam observações anteriores de que na prática clínica, o tratamento da hipertensão é frequentemente abandonado e implementado de forma deficitária ao longo do tempo.

Praticamente um em cada cinco (19.5%) doentes ou não inicia tratamento, ou fá-lo com um atraso considerável (em média, praticamente um ano e meio depois de ter recebido

uma primeira prescrição) ou descontinua completamente o tratamento logo após a primeira dispensa.

O risco de descontinuação é mais acentuado durante o primeiro ano de tratamento, principalmente para os doentes mais jovens. Diferentes fatores poderão contribuir para esta maior descontinuação nos mais jovens. Desde logo, a natureza assintomática da HTA, que associada a eventuais efeitos secundários da própria TAH poderão contribuir para uma menor perceção da necessidade de realizar tratamento. Por outro lado, o tratamento da HTA não depende apenas da prescrição de medicamentos. A modificação dos estilos de vida poderá ter impacto positivo na evolução da doença, particularmente nos doentes mais jovens, com provavelmente menos fatores de risco cardiovasculares. Nesse sentido, importa avaliar em estudos futuros o impacto da modificação dos estilos de vida no controlo da pressão arterial e, dessa forma, a sua relação com a adesão à TAH.

Um achado particularmente relevante nesta tese é a de que a larga maioria dos doentes utiliza a TAH de forma descontinuada, interrompendo-a e reiniciando-a de forma frequente. Isto implica que a decisão de descontinuar tratamento não é uma decisão definitiva. No entanto, é particularmente preocupante no caso de um doente que efetivamente necessita de tratamento, não realizá-lo durante períodos longos e consecutivos. Nesse sentido, os prescritores deverão de forma ativa tentar monitorizar a utilização da TAH por parte dos doentes, de forma a proactivamente tentar identificar possíveis limitações à utilização dos medicamentos prescritos.

Na prática clínica é relativamente comum que, na ausência de controlo de determinada doença, o prescritor responda aumentando as doses dos medicamentos prescritos ou até mesmo modificando ou acrescentando novos medicamentos. No entanto, a falta de controlo de determinada doença é, muitas vezes, o resultado da falta de adesão à terapêutica e não da falta de efetividade do tratamento. Portanto, na falta de efetividade de um tratamento, o prescritor deve colocar a questão: será que o medicamento falhou na sua atividade ou será que o doente falhou a sua utilização?

Se praticamente um em cada dois medicamentos prescritos não são dispensados numa farmácia (taxa de não-adesão primária = 41.5%), o que se reflete num MPR médio de

43.6±23.1%, então os potenciais benefícios da TAH não serão completamente realizados, diminuindo a proteção contra as complicações da hipertensão não controlada e aumentando o risco cardiovascular nestes doentes.

A baixa adesão à TAH encontrada nesta tese – em todas as suas componentes – é particularmente preocupante, já que esta condição contribui grandemente para o peso da morbilidade e mortalidade das DCV em Portugal.

Até à realização desta tese, a adesão à TAH tinha sido avaliada, em Portugal, quase exclusivamente na componente da implementação. A adesão à terapêutica é um processo dinâmico, influenciado por múltiplos fatores em diferentes momentos temporais e como tal, a sua avaliação transversal e descrição num único número ou taxa ou percentagem, corresponde a uma simplificação de uma realidade complexa, com pouco impacto na definição de programas de intervenção nos padrões de utilização dos tratamentos. Os fatores que influenciam a decisão de iniciar um tratamento não são necessariamente os mesmos que determinam a sua (eventual) descontinuação, tal como foi demonstrado nesta tese.

A avaliação da adesão à terapêutica é fundamental para uma melhor compreensão dos fatores relacionados com a não-adesão, para habilitar, de forma eficiente, a identificação de medidas que visem a sua melhoria e, consequentemente, a melhoria dos resultados em saúde, uma vez que a adesão relaciona-se com os *outcomes* clínicos e os custos com os cuidados de saúde prestados a estes doentes.

O relatório da Organização Mundial da Saúde sobre adesão à terapêutica nas doenças crónicas faz eco da sugestão de Haynes et al., de que aumentar a efetividade das medidas que promovam uma maior adesão à terapêutica poderá ter um maior impacto nos cuidados de saúde – a nível terapêutico mas também a nível económico – que qualquer melhoria no tratamento médico propriamente dito.

Nesse pressuposto, os benefícios da utilização das bases de dados de prescrições médicas e dispensa/faturação das farmácias comunitárias devem ser considerados não só na avaliação da adesão à terapêutica mas também na monitorização da efetividade das medidas que visem a promoção de adesão.

Embora o estudo da adesão à terapêutica com recurso a bases de dados eletrónicas apresente algumas limitações, como, por exemplo, a incapacidade de garantir que o doente efetivamente tomou o medicamento levantado na farmácia, as grandes bases de dados revelam-se particularmente úteis na avaliação da adesão às classes terapêuticas indicadas para os tratamentos crónicos. Quando não exista a possibilidade de adquirir os medicamentos a partir de outras fontes não capturadas na base de dados, a especificidade desta metodologia para detetar os doentes que não tomam os medicamentos prescritos é, efetivamente, muito alta

Num momento em que a prescrição eletrónica de medicamentos é obrigatória em Portugal e o processo de conferência das receitas médicas se encontra centralizado num centro de conferências de faturas nacional, esta deverá ser nos próximos tempos, uma das principais fontes de informação na investigação da adesão à terapêutica.