

# Linkage between electronic prescribing data and pharmacy claims records to determine primary adherence: the case of antihypertensive therapy in the Lisbon and Tagus Valley Region, Portugal

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**Background:** Hypertension (HT) is highly prevalent and a major risk factor for cardiovascular disease. Over 42% of Portuguese adults have HT. Even though the benefits of antihypertensive (AHT) drugs have been demonstrated, HT control remains inadequate. One major reason is that patients often fail to take their medications as prescribed. This paper aims to determine primary adherence to AHT therapy in newly diagnosed and treated hypertensive patients in Primary Health Care (PHC) units of Lisbon and Tagus Valley Health Region.

**Methods:** This study reports data from a population-based, retrospective, cohort study from patients diagnosed with HT in PHC units of Lisbon and Tagus Valley Region from 1 January to 31 March 2011, with no prior use of AHT drugs. Primary adherence rate was expressed as number of claims records/total number of prescriptions records. Data were collected from SIARS for each patient during a 2-year period.

**Results:** Overall primary adherence rate was 58.5%, increasing with age. Rates were higher for men, living in the Lisbon Metropolitan Area and diagnosed with uncomplicated HT. Drugs acting on the renin–angiotensin system had the highest rates, increasing for fixed-dose combinations and diminishing with the increase of cost for the patient.

**Conclusions:** Overall, almost 1 out of 2 prescribed AHT drugs were not dispensed. Until this study, little was known in Portugal about primary adherence. Our findings imply that the potential benefits of AHT therapy cannot be fully realized in this population.

**Key words:** antihypertensive therapy, medication adherence, primary adherence

## Introduction

Hypertension (HT) is an important risk factor for the development of cardiovascular morbidity and mortality.<sup>1–3</sup> About half of all cardiovascular disease (CVD) combining morbidity and mortality, can be attributable to high blood pressure (BP).<sup>1–3</sup>

Despite these consequences and the wide range of effective, well-tolerated medications used in HT treatment, BP control continues to be inadequate and up to two thirds of patients with HT are not successfully treated.<sup>4</sup> In Portugal, the PHYSA (Portuguese Hypertension and Salt) Study shown that 23.4% of the Portuguese with HT are unaware of their condition, and overall, among hypertensive patients, only 42.5% reach a controlled BP below 140/90 mm Hg.<sup>5</sup>

The precise reasons for patients not achieving control of their BP despite being treated are not completely clear yet. Still, 3 main causes of the low rate of BP control have been identified: (i) physician inertia; (ii) patient low adherence to treatment; and (iii) deficiencies of health care systems in their approach to chronic diseases,<sup>2</sup> being low adherence, perhaps the most important cause.<sup>6,7</sup> Prior studies<sup>8–15</sup> have demonstrated poor adherence in hypertensive patients to be associated with an increased risk for CVD.

Medication adherence is often measured using claims-based electronic pharmacy databases.<sup>7–9,16–18</sup> Such studies have

demonstrated that patients typically obtain less medication than they have been prescribed,<sup>15,17,19–24</sup> and many patients stop taking medications soon after filling the first prescription.<sup>25</sup> Primary adherence therefore refers to a new prescribed medication being dispensed at a pharmacy within a defined number of days after it was prescribed.<sup>19,26–30</sup>

In Portugal, since 2010 electronic prescribing (e-prescribing) is mandatory for all National Health System (NHS) reimbursed drugs regardless the health care providing system. E-prescribing creates an electronic record of the written prescription, and so its use provides an opportunity to determine primary (non)-adherence, and to examine correlates of different rates.<sup>19,27,30,31</sup>

Little is known in Portugal about the rate of prescribed medications that are written by a physician yet never acquired by the patient in a community pharmacy. To our best knowledge this was the first study in the country to measure primary adherence to antihypertensive (AHT) drugs linking prescription and pharmacy claims data.<sup>32</sup>

## Objective

To determine primary adherence to AHT therapy in newly diagnosed and treated hypertensive patients in Primary

## Key messages

- Medication nonadherence is a main cause for low rate of blood pressure control.
- Electronic prescription provides an opportunity to determine primary adherence.
- Data show that 41.5% of all prescribed antihypertensive drugs were not dispensed.
- Primary adherence is higher for fixed-dose combinations.
- Cost for the patient is a crucial factor for nonadherence.

Health Care (PHC) units of Lisbon and Tagus Valley Health Region.

## Methods

### Study design and study population

We have conducted an observational study, more specifically a retrospective cohort study. Study population consists of all newly diagnosed adult patients with HT, in terms of codes k86—HT, uncomplicated—and k87—HT, complicated—of the International Classification of Primary Care, 2nd ed. (ICPC-2)<sup>33</sup>, in the PHC units of Region of Lisbon and Tagus Valley from 1 January to 31 March 2011. For these patients, data on all e-prescriptions for AHT written from 1 January 2011 to 31 December 2012 were collected.

E-prescribing and claims data were provided for the 24-month study period and for the 6 months prior (i.e. beginning 1/07/2010) to account only for new users of AHTs—10,204 in total. Claims data were additionally collected for 6 months after (i.e. ending 30/06/2013), since a prescription can be filled in Portugal within 6 months after it was prescribed.

### Data sources

We used 2 sources of data: e-prescribing records from the PHC units in the Lisbon and Tagus Valley region and pharmacy claims records. The regional health administration of Lisbon and Tagus Valley accounts for about 13% of the Portuguese territory and 34.6% (3.7 million) of its population.

Within the PHC units, all prescription information is collected centrally. Pharmacy claims are submitted also electronically to a centralized reimbursement system.

Prescriptions and claims data were drawn from SIARS—Information System of the Regional Health Administration of Lisbon and Tagus Valley, which is an administrative database, developed to facilitate analysis and monitoring of PHC units activity and production. This automated system includes information on diagnosis made and registered within the PHC network, as well patients demographic and administrative data.

Prescription data include all e-prescriptions issued within the PHC units of Lisbon and Tagus Valley region, regardless of whether they were eventually filled (i.e. dispensed to the patient) or not. As extracted from SIARS, each record includes a unique identification number, encoded prescribing clinician identification, patient identification, and prescription date. Drugs are identified by ATC code and national drug code, generic/brand name, strength, pharmaceutical form, presentation (package size) and number of packages prescribed, and costs (for the NHS—69% of the reference price within a homogeneous group, when applicable, or 69% of the recommended retail price when the drug is not

included in a homogeneous group and for the patient—the difference for the recommended retail price). Patient identification number allows for linkage within SIARS to collect patient's personal information (age, gender, housing parish code—used as a proxy of patient's buying power—and diagnoses code), as well as prescribers information, namely if the PHC physician is assigned or not to the patient.

Pharmacy claims includes data on prescriptions that were filled and reimbursed by the NHS. The claims data include the e-prescription identification number, encoded patient identification, prescription fill date, and costs (for the NHS and for the patient). Dispensed drugs are identified with the same information as prescribed drugs.

All identifiable individual characteristics were removed from the data before transfer to the researchers, which were not evolved in data collection. This study was approved by the ethics committee of ARSLVT.

### Linking pharmacy claims to e-prescribing records

Each prescription has its unique individual identification number that was used to link pharmacy claims to e-prescribing records. Since each prescription can include up to 4 different drugs, we have also used the ATC code to match both files. It's the patient's decision which prescribed drugs within the same prescription are dispensed at the pharmacy. In that note, a drug was defined as dispensed if there was a match between both files of the prescription individual identification number and the ATC code at any time prior to the end of our data.

### Primary adherence measurement and statistical analyses

Primary adherence rate was expressed as the number of pharmacy claims records divided by the total number of prescriptions records. Each claim corresponds to a single AHT drug. Thus, the unit of analyses was the AHT drug, not the patient.

We compared primary adherence rates across patients characteristics, such as gender, age, region, buying power, and diagnosis of HT (ICPC-2 codes k86 or k87), as well across drug classes and other drug characteristics, such as its classification as generic or brand name drug and cost for the patient. Bivariate analysis was conducted to determine which characteristics were related to primary adherence. Categorical variables were analyzed using the chi-square test with a level of significance of 5%. All analyses were conducted with the SPSS statistical software package version 23.

## Results

A total of 68,206 e-prescriptions for 182,841 AHT drugs were written during the study period for these patients.

**Table 1.** 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 ( $\pm$ SD)	60.5 $\pm$ 12.8	61.5 $\pm$ 13.2	61.0 $\pm$ 13.0
18–44	482 (10.4%)	548 (9.9%)	1,030 (10.1%)
45–64	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) <sup>a</sup>			
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%)
$\geq$ 200	556 (12.0%)	737 (13.3%)	1,293 (12.7%)
ICPC-2 code <sup>b</sup>			
k86	3,147 (91.3%)	3,971 (95.0%)	7,118 (93.3%)
k87	301 (8.7%)	210 (5.0%)	511 (6.7%)

NUTS, Nomenclatura das Unidades Territoriais para Fins Estatísticos.

<sup>a</sup>Data missing for 9 patients.

<sup>b</sup>Data missing for 2,575 patients.

**Table 1** shows baseline characteristics of patients enrolled in the study.

The overall primary adherence rate was 58.5%, corresponding to 107,024 ATH drugs dispensed at community pharmacies, meaning 41.5% primary nonadherence.

When prescriptions were analyzed by patient characteristics (**Table 2**), overall primary adherence increased with age ( $P < 0.001$ ), and it was higher for men ( $P = 0.020$ ). For patients living in the Lisbon Metropolitan Area, 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  $\geq 100$ , 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 uncomplicated HT (ICPC-2 code k86) ( $P = 0.001$ ). However, the results for these 2 variables should be looked at carefully because they are not complete for every prescription, which may be leading to an overestimation of the adherence rates.

The prescriber itself—patient's family doctor or not—does not seem to affect the adherence rate. 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, angiotensin receptor blockers (ARBs), alone or in fixed-dose combinations with a diuretic or a calcium channel blocker (CCB), angiotensin-converting enzyme inhibitors (ACEIs) in fixed-dose combinations and beta-blockers (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 3**).

Both ARBs and ACEIs in fixed-dose combinations had higher primary adherence rates compared with their “plain” formulations. Overall, we found no differences in the primary adherence rates of prescribed generic or brand name drugs ( $P = 0.710$ ). However, when we analyzed 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.

The cost for the patient of the prescribed drug influences its acquisition. An increase in cost for the patient 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 renin–angiotensin system and CCBs (**Fig. 1**).

## Discussion

Medication non- or sub optimal adherence reduces the effectiveness of essential medications and has been highlighted as a significant obstacle in achieving better patient outcomes,<sup>7,25,34</sup> which translates in increased health care costs. However, assessment of adherence and interventions to improve adherence have been largely conditional on patients filling their initial prescriptions, and have failed to accurately account for primary nonadherence. The increasing use of e-prescribing creates the opportunity to measure primary nonadherence in larger populations.

To date there has been a limited body of research addressing primary adherence, including in AHT therapy. Ax and Ekedahl evaluated 44,607 e-prescriptions in a Swedish population and found a nonadherence rate of 2.5%.<sup>35</sup> Fischer et al. evaluated 195,930 e-prescriptions and found a

**Table 2.** Primary adherence, by patients characteristics.

Patients characteristics	Prescribed drugs	Dispensed drugs (%)	P
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
18–44	12,113	6,662 (55.0%)	
45–64	76,952	44,239 (57.5%)	
65 or more	93,776	56,123 (59.8%)	
Region (NUTS III) <sup>a</sup>			<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 <sup>a</sup>			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 <sup>b</sup>			0.001
k86	134,778	84,059 (62.4%)	
k87	12,609	7,386 (58.6%)	

<sup>a</sup>Data missing for 171 prescriptions records.

<sup>b</sup>Data missing for 34,454 prescriptions records.

**Table 3.** Primary adherence, by drug class.

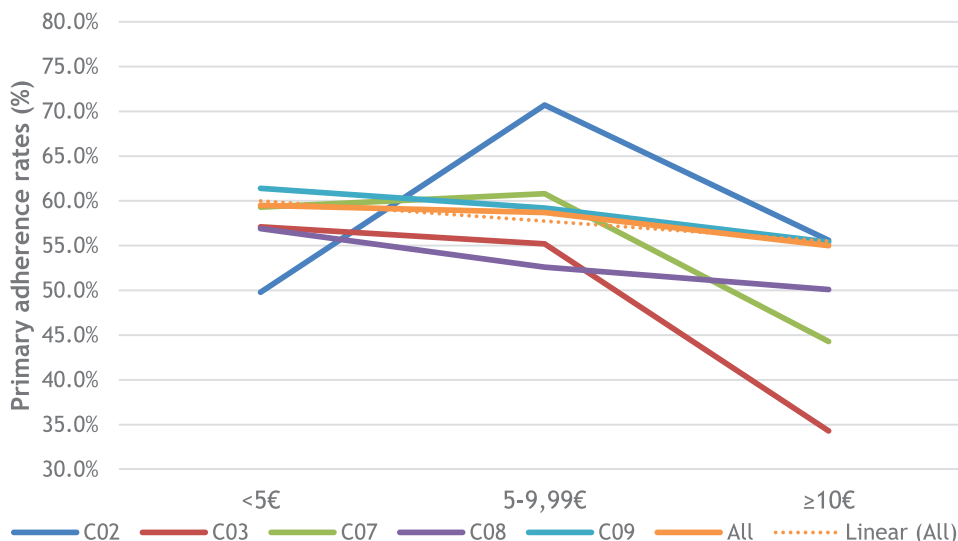
Drug class	Prescribed drugs		Dispensed drugs (primary adherence rate)		
	Brands	Generics	Brands	Generics	Total
Diuretics					
Plain	7,510	11,338	4,204 (56.0%)	6,603 (58.2%)	57.3%
Combination	2,028	631	1,108 (54.6%)	341 (54.0%)	54.5%
BBs	9,718	10,053	5,803 (59.7%)	5,862 (58.3%)	59.0%
CCBs	9,160	10,053	5,386 (58.8%)	5,376 (53.5%)	56.0%
ACEIs					
Plains	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%

nonadherence rate of 22%.<sup>22</sup> Another study found that patients being started on treatment for HT failed to fill new prescriptions 17% of the time.<sup>27</sup> Our study in Portugal found a higher primary nonadherence rate compared with these others studies using claims data.

To our best knowledge, this was the first study in Portugal to measure primary adherence rates for AHT drugs, linking e-prescribing records and pharmacy claims data. In this study, we found that 41.5% of e-prescribed drugs were never dispensed. We evaluated only new users of AHT drugs within

the PHC network of Lisbon and Tagus Valley region. Previous studies have demonstrated lower medication adherence rates when using a new prescription cohort.<sup>21,31</sup>

The high rate of nonadherence to AHT drugs is an especially alarming finding; this condition contributes greatly to the burden of mortality and morbidity from CVD in Portugal. It has previously been shown that many patients with HT either lack awareness of their diagnoses or are not receiving treatment.<sup>5,7</sup> If more than 40% of prescribed AHT drugs are not dispensed, their potential benefits will



**Fig. 1.** Effect of out-of-pocket costs in primary adherence rates, by drug class. C02—AHTs; C03—diuretics; C07—BBs; C08—CCBs; C09—agents acting on the renin-angiotensin system.

not be realized. For that reason, 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.<sup>30</sup>

Several factors were associated with lower primary adherence. Interventions aimed at improving BP control must address the needs and challenges of patients who are first initiated on their medications. Numerous studies<sup>9,19,22,27,36</sup> found that increased out-of-pocket costs are associated with decreased use of prescription drugs, even for highly effective medications, such as the ones used on HT, which was also found in our study. Moreover, adherence rates were higher for generic drugs compared with brand name, and therefore more expensive, drugs. Shrank et al.<sup>37</sup> also found a higher adherence rate for generic drugs.

We had limited patient-specific information. Still, overall primary adherence increased with age ( $P < 0.001$ ), and it was higher for men ( $P = 0.020$ ). Other studies found that women were less likely than men to fill prescriptions.<sup>19,27</sup>

Unmeasured patient and physician factors, such as the extent of physician-patient communication and education about prescriptions are likely to influence adherence. In our study, although we have found slightly higher adherence rates when the drug was prescribed by the physician assigned to the patient, that was not statistically significant.

A meta-analysis conducted by Kronish et al.<sup>38</sup> found a remarkable degree of consistency in the demonstration of superior adherence to ARBs and ACEIs and inferior adherence to diuretics. We found low adherence rates for diuretics and CCBs. These lowest adherence rates of diuretics and CCBs are possibly due to increased adverse effects of drugs from these classes, as found by other authors.<sup>38,39</sup>

Adherence rates of fixed-dose combinations of ACEIs and ARBs with other drugs were higher compared with the plain formulations of those classes. These findings support that the use of low-dose combinations favors adherence probably because of the smaller side effects compared with full-dose therapy.<sup>40</sup>

## Limitations

There are limitations that must be considered when interpreting these results. We have limited data on patient and physician characteristics, which limits our ability to explain the causes of nonadherence. The prescription data refer only to the PHC network and patients may have received prescriptions by other providers, including specialist and hospital outpatient settings that are not captured by SIARS, which may lead us to under- or overestimate the rate of adherence. Any other data errors in the prescribing and/or claims records could lead to a drug to being falsely labelled as not dispensed; this type of mis-classification of the outcome could lead us to overestimate nonadherence.

Also, as Karter et al.<sup>20</sup> pointed out, claims-based research is subject to mis-classification 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 nonadherence may be overestimated.

## Conclusions

Until this study, little was known in Portugal about primary adherence to AHT therapy, especially at a population level. Overall, almost 1 out of 2 prescribed AHT drugs were not dispensed (overall primary nonadherence rate = 41.5%). Our findings imply that the potential benefits of AHT therapy in lowering cardiovascular risk and the consequences of uncontrolled HT, cannot be fully realized in this population. Further research will be needed to confirm and understand the causes of these findings and to develop interventions to improve primary adherence.

Despite the fore mentioned limitations, this study identified several modifiable determinants of primary adherence

to AHT drugs 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 their cost and the different characteristics that may influence patient's adherence to medication.

Our ability to link prescribing data to filled claims allowed us to measure primary nonadherence, which was not possible until recently. This research will be instrumental in developing interventions that encourage patients to initiate medications which when prescribed, are adhered to, leading to a full course of chronic therapy.

Naturally, further research will be needed to confirm and better understand the causes of nonadherence to AHT therapy, specially in the PHC setting, by evaluating other known risk factors unmeasured within this paper, focusing on the individual patients behavioural intentions, barriers, and subjective norms.

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## Ethical approval

The study was approved by the ethics committee of Lisbon and Tagus Valley Regional Health Administration.

## Conflict of interest

None declared.

## Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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