# 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 file with the prescriptions records for the 29,896 patients and the other file with the claims records for 28,121 of those patients.

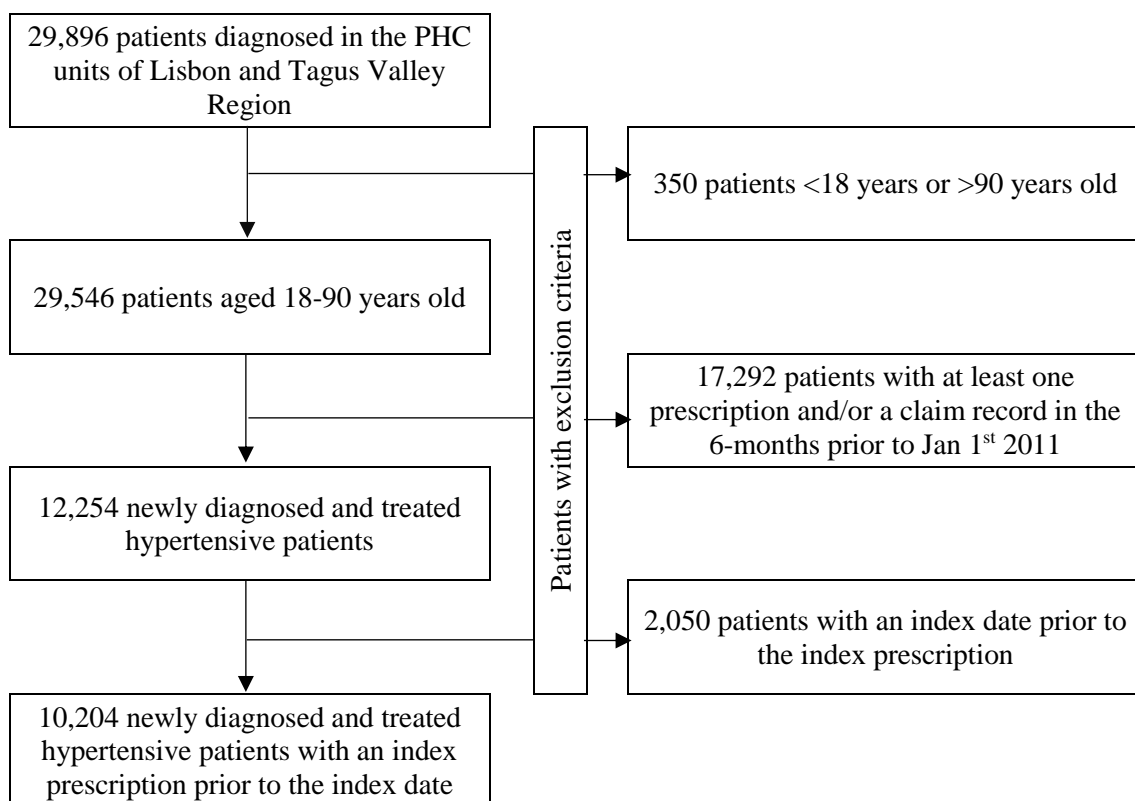Figure 5 shows the flow chart of the application of the exclusion criteria.



**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, the 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 the 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 only 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 able to determine individual's buying power, extracting that information from the PORDATA website[174]. 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 the incidence of hypertension in this Region, 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.

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[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).
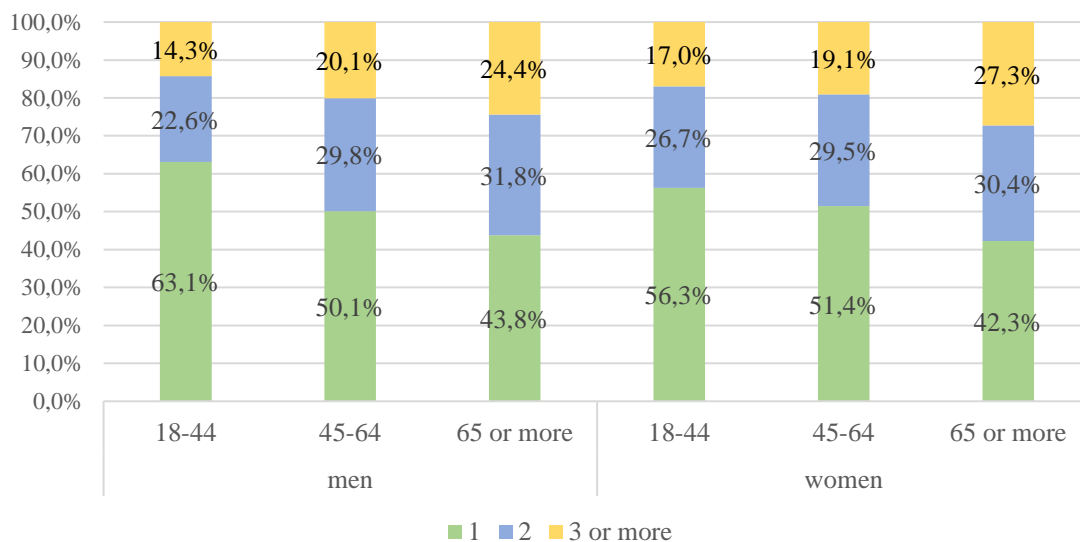


**Figure 6. Number of prescribed AHT drugs, by age group and gender**

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

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[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, $2^{nd}$ and $3^{rd}$ 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).
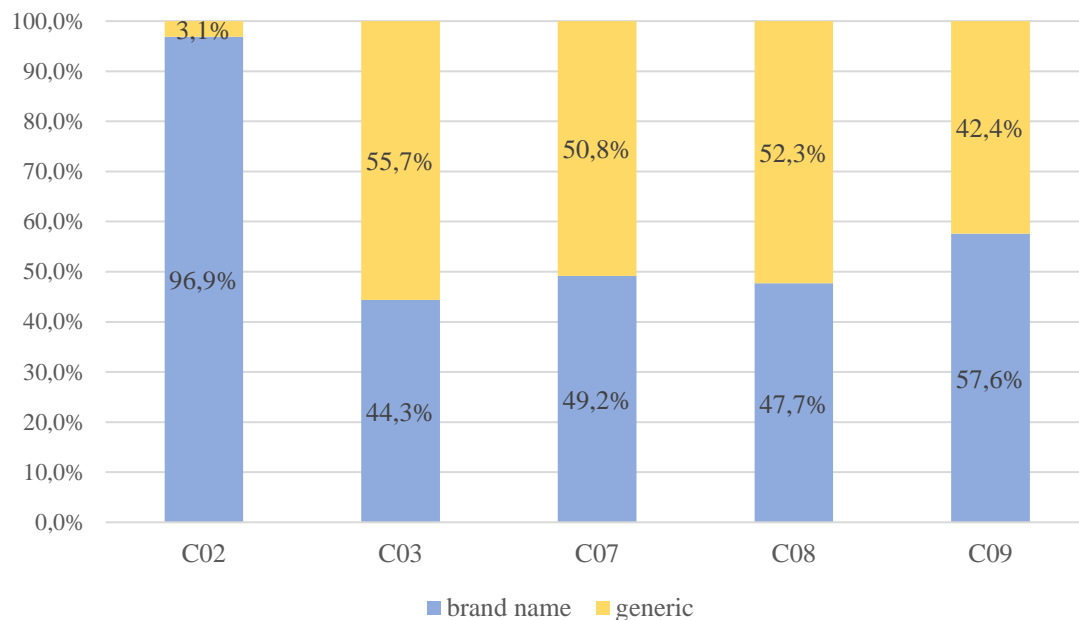


**Figure 7. Generic and brand named AHT drugs prescribed during the observation period**
**Legend:** C02 – Antihypertensives; C03 – Diuretics; C07 – Beta blocking agents; C08 - Calcium channel blockers; C09 - Agents acting on the renin-angiotensin system

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 AHTs | 126 (2.7%) | 154 (2.8%) | 280 (2.7%) |

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

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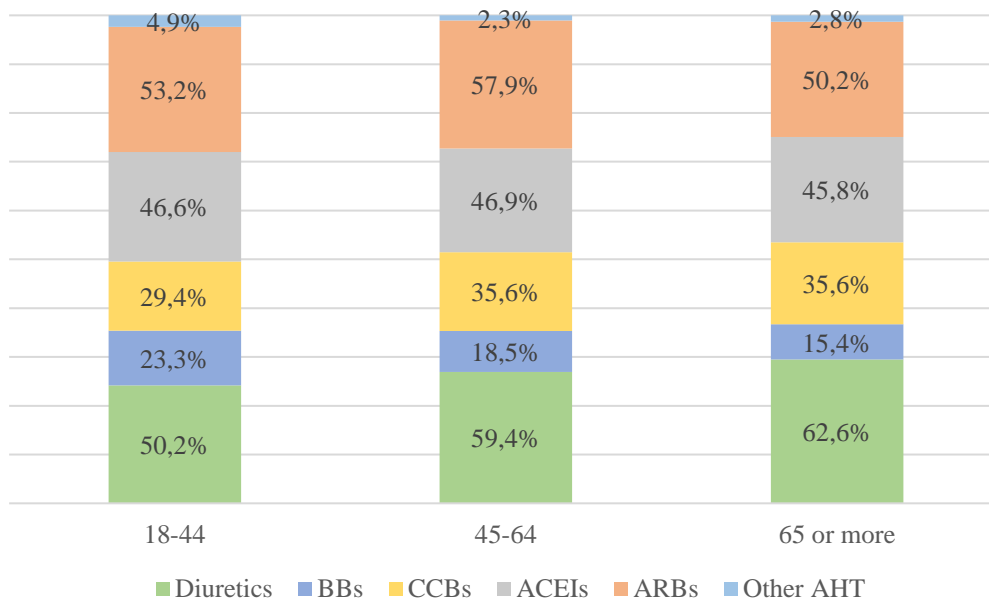
**Figure 8. Proportion of AHT drug classes prescribed per patient, by age group**

**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 – Antihypertensives

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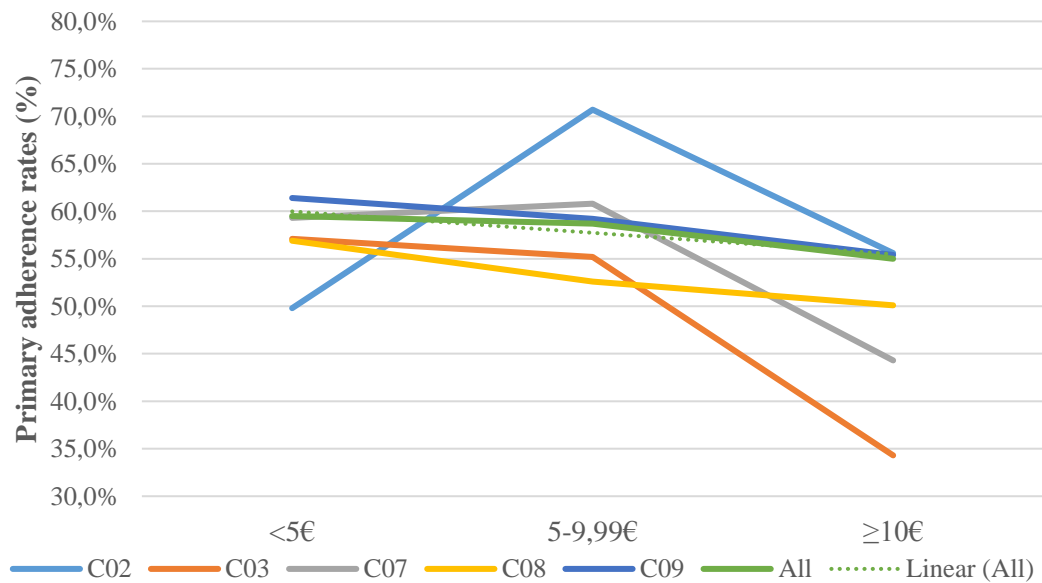
**Figure 9. Effect of out-of-pocket costs in primary adherence rates, by drug classes**

**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 – Antihypertensives.

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 physicians (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).
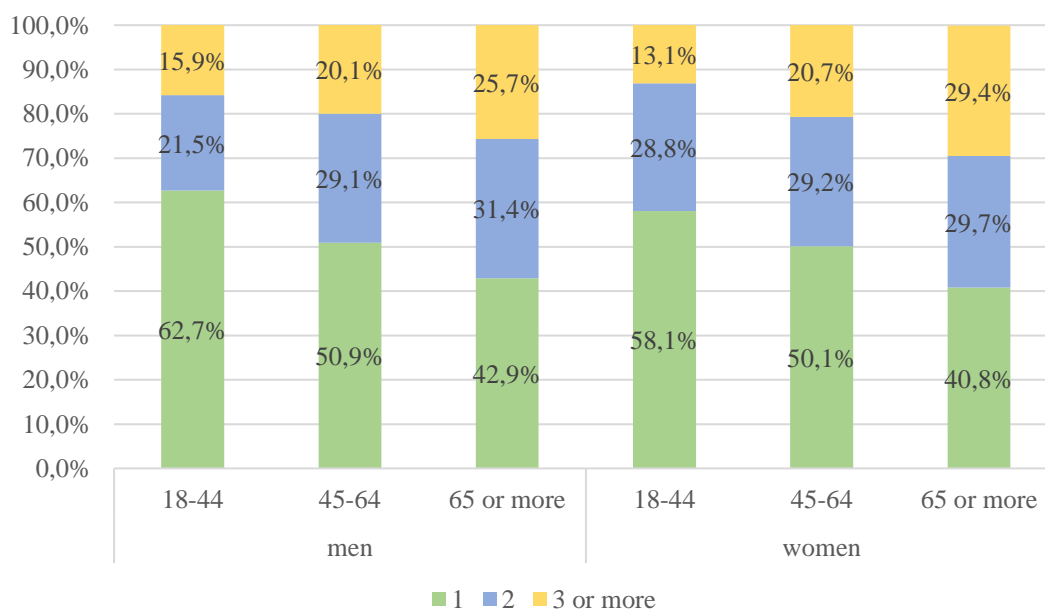


**Figure 10. Number of AHT drugs dispensed per patient, by age group and gender**

### 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 – Antihypertensives; 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).
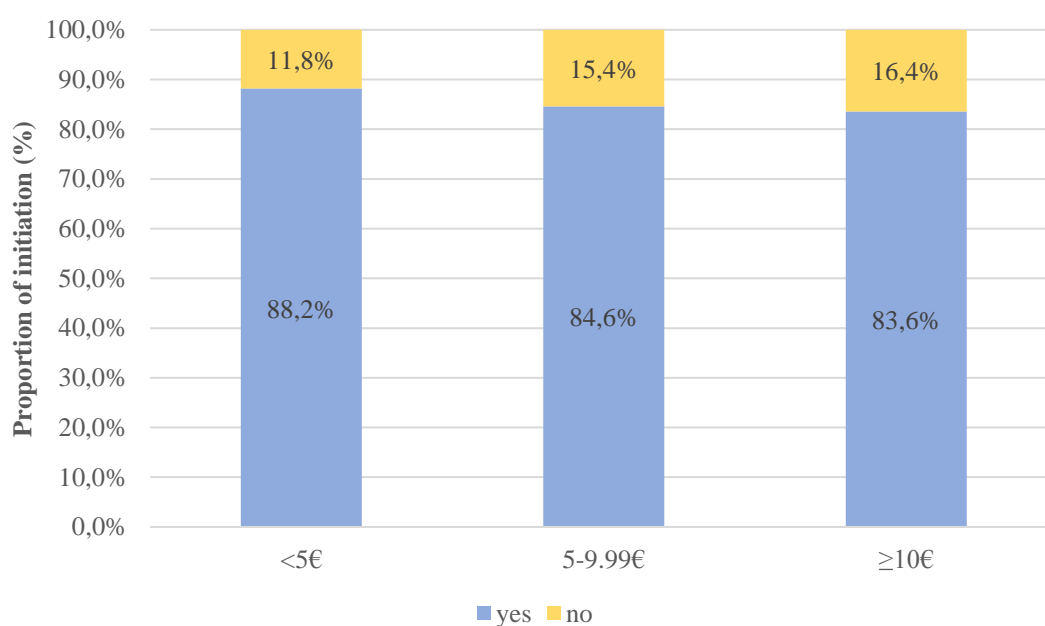


**Figure 11. Initiation of AHT therapy, by out-of-pocket cost**

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).
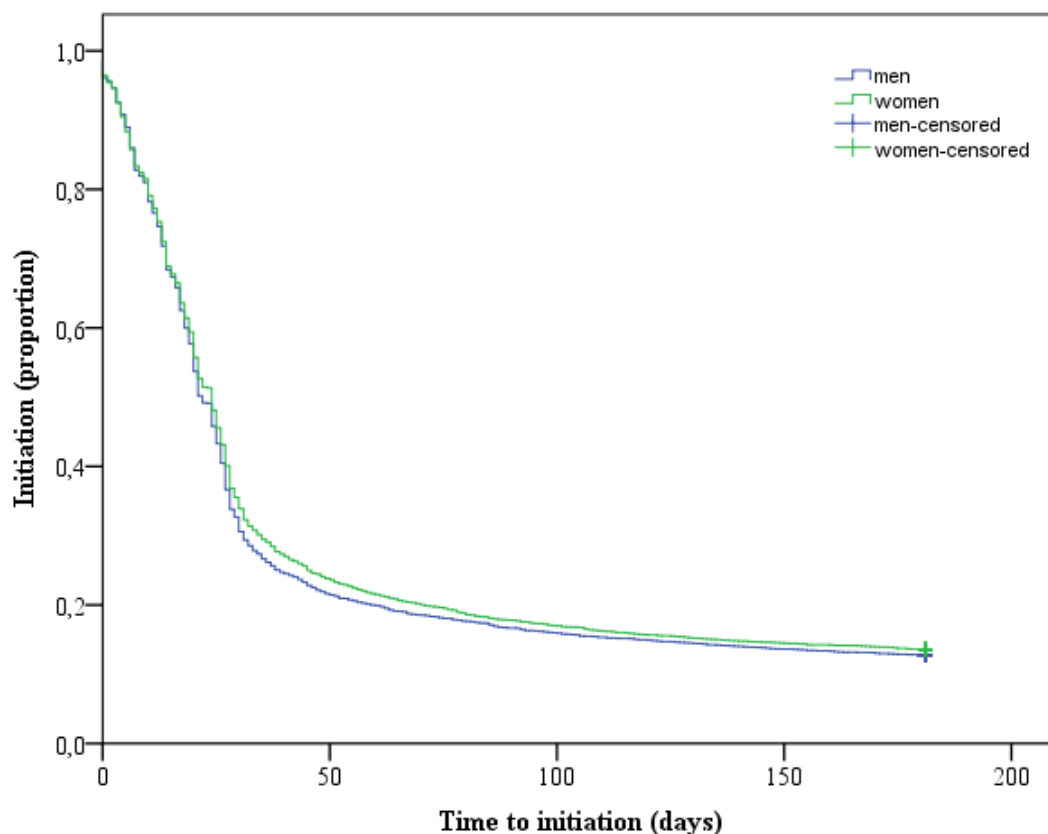


**Figure 12. Kaplan-Meier curve of initiation of AHT therapy, by gender**

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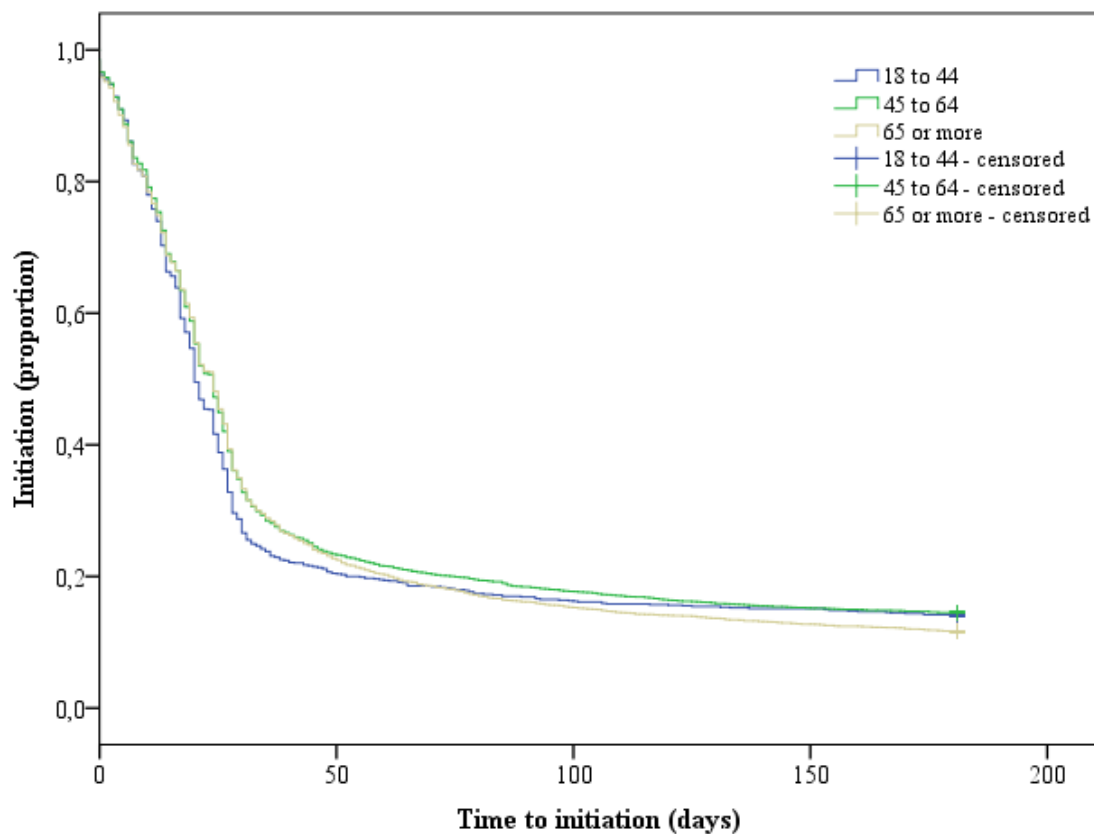
**Figure 13. Kaplan-Meier curve of initiation of AHT therapy, by age group**

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; ICPC-2 – International Classification for Primary Care, 2nd edition

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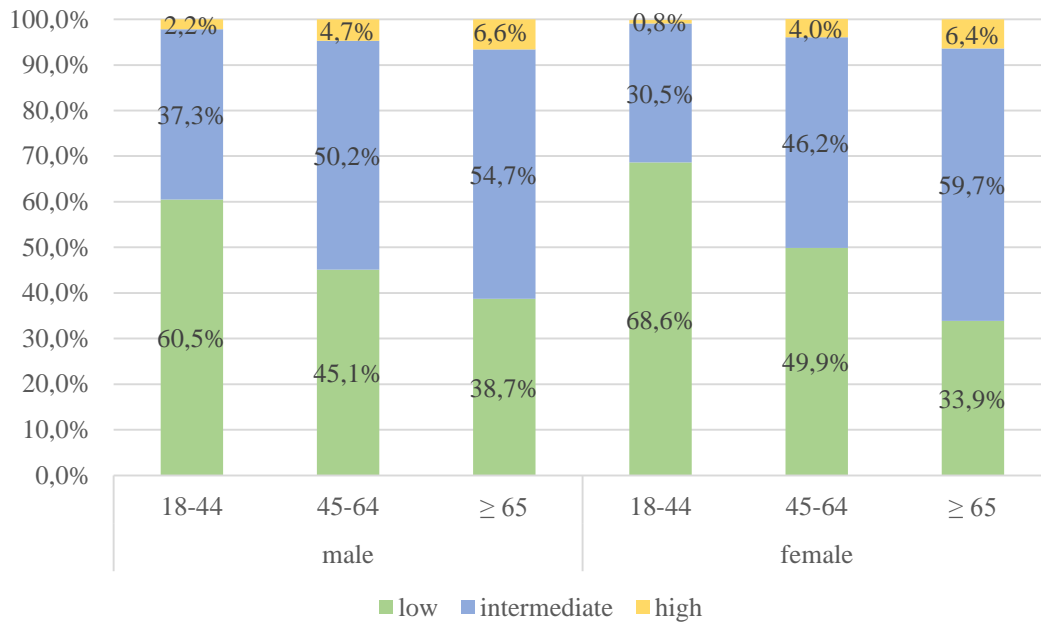
**Figure 14. Implementation of AHT therapy, by age group and gender**

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).
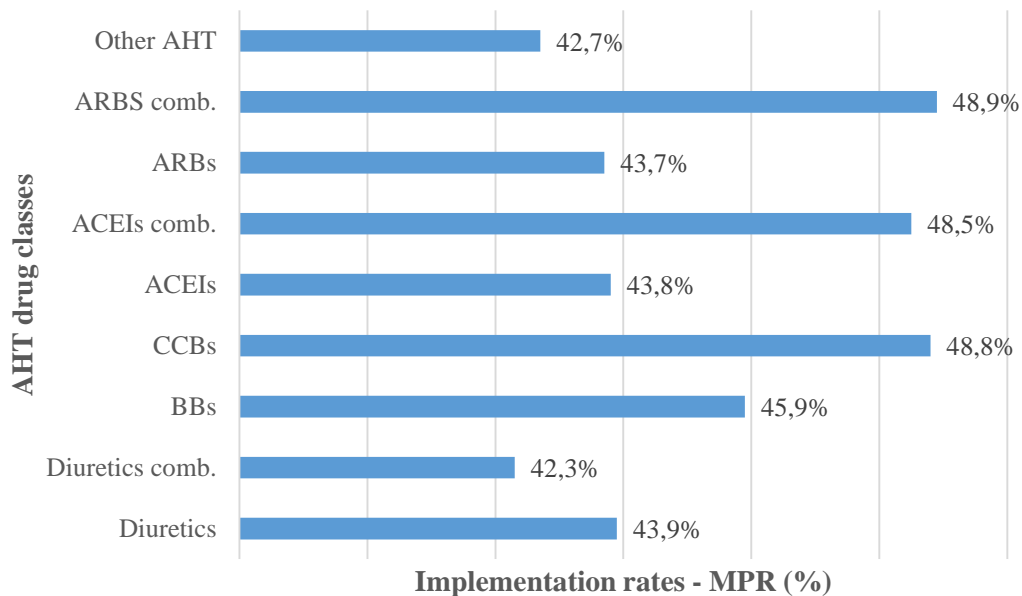
**Figure 15. Implementation of AHT therapy, by drug classes**

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

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,

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[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.

had no significant association to low adherence after adjustments for all potential predictors (Table 16).

**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 – 5$^{th}$ 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% $\geq$ 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).
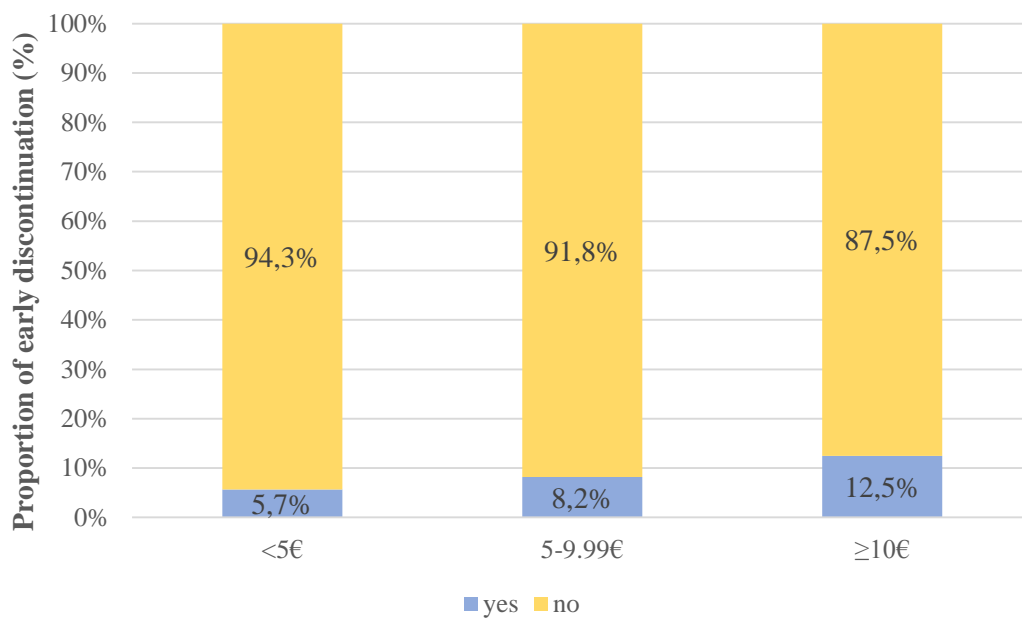
**Figure 16. Early discontinuation of AHT therapy, by out-of-pocket cost**

### 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).
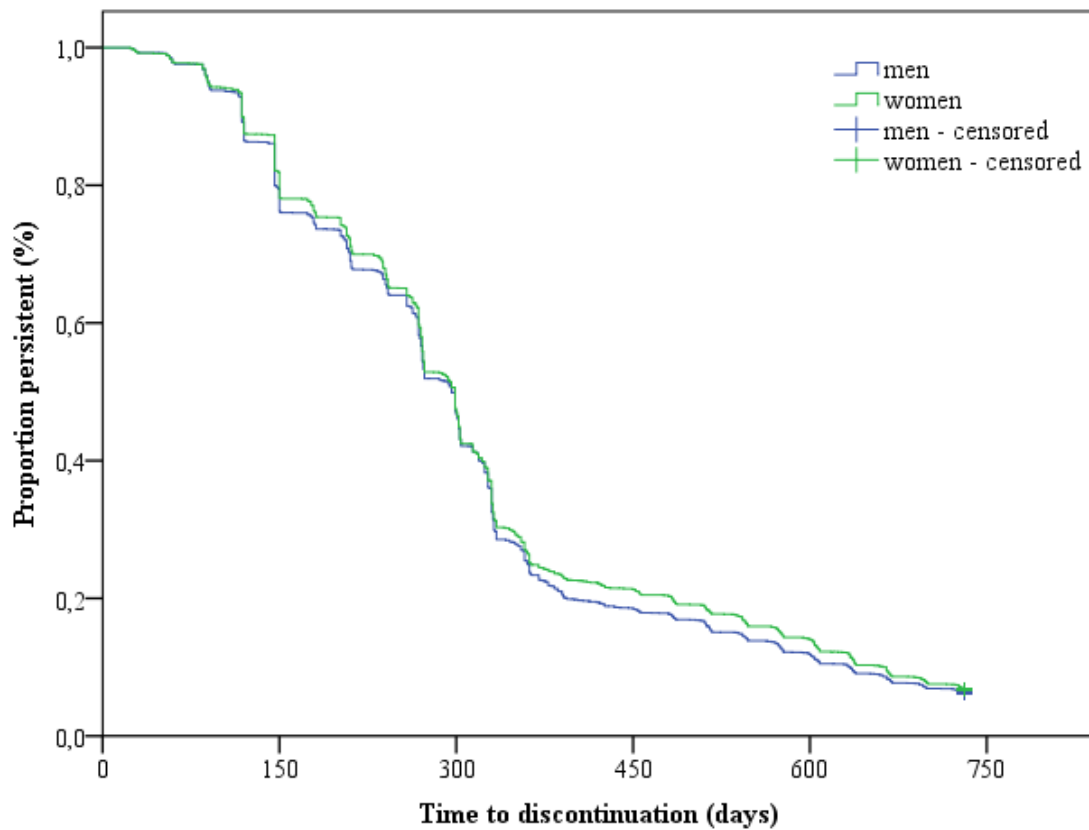
**Figure 17. Persistence to AHT therapy, by gender**

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).
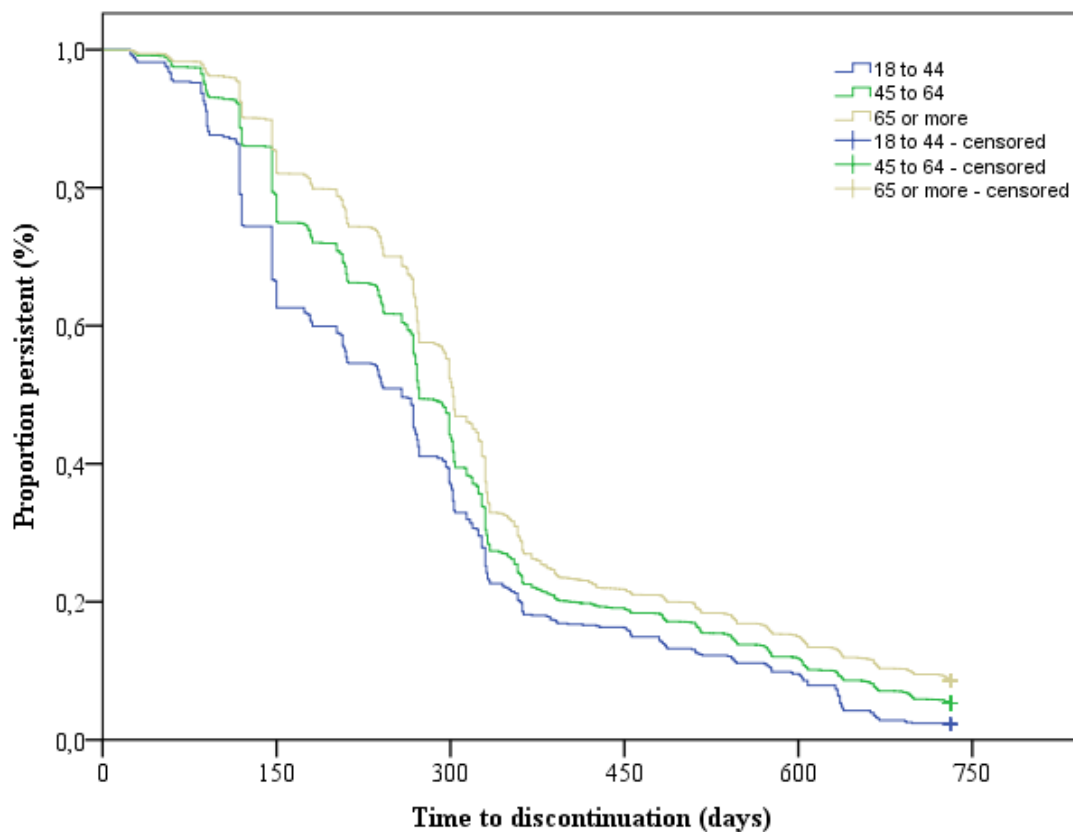
**Figure 18. Persistence to AHT therapy, by age group**

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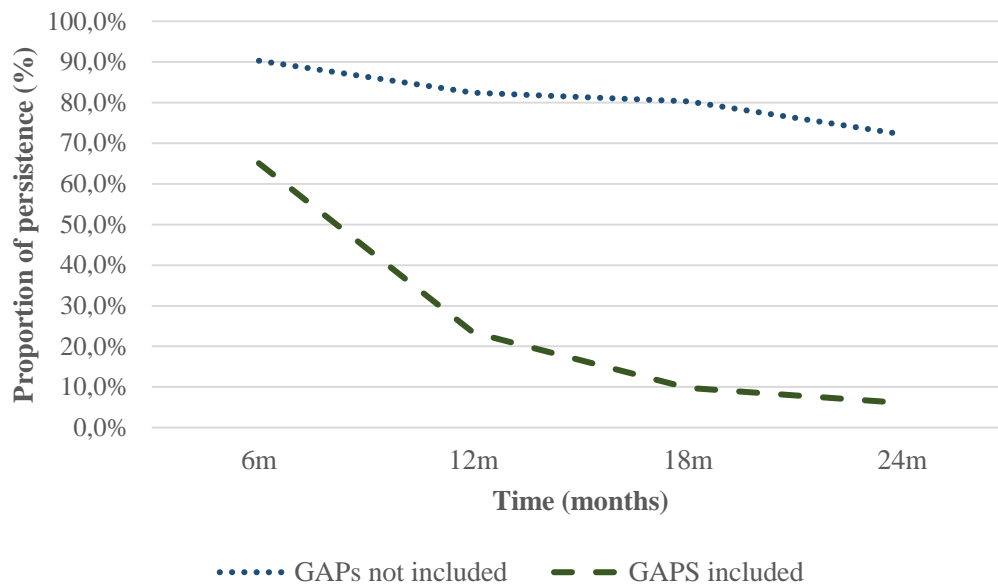
**Figure 19. Persistence to AHT therapy considering the existence of a grace period of 90 days**

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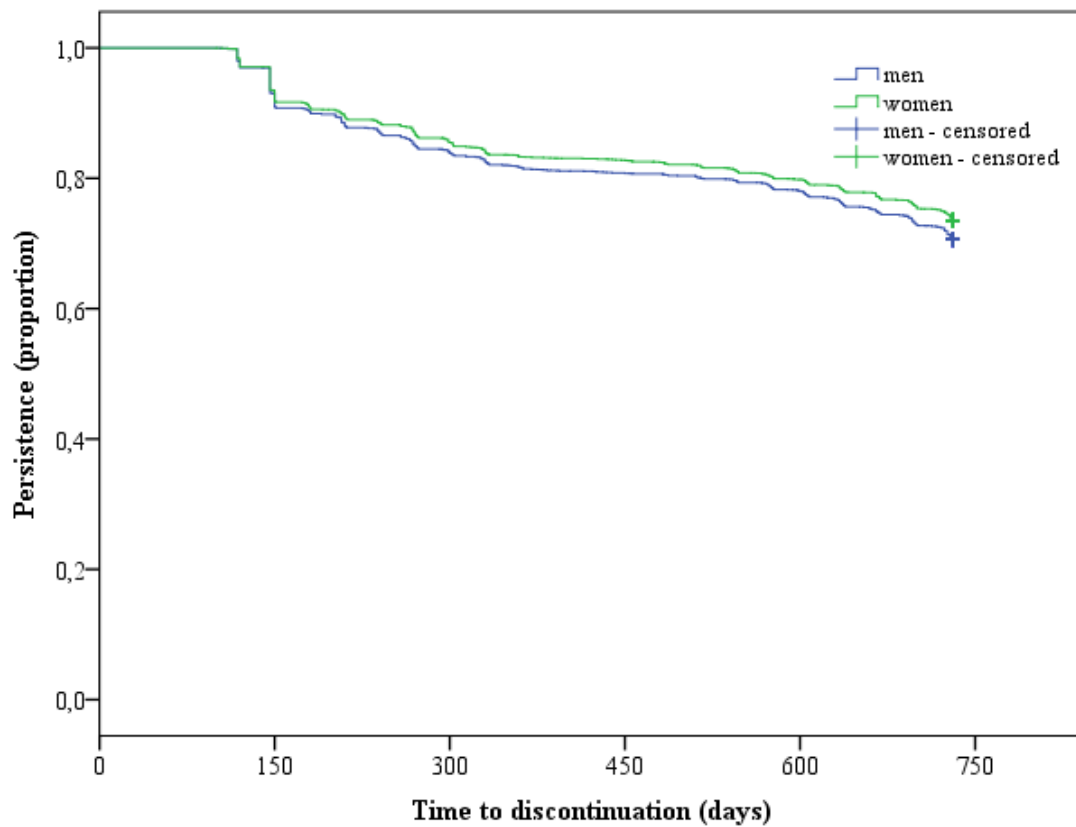
**Figure 20. Persistence, including reinitiation, to AHT therapy by gender**

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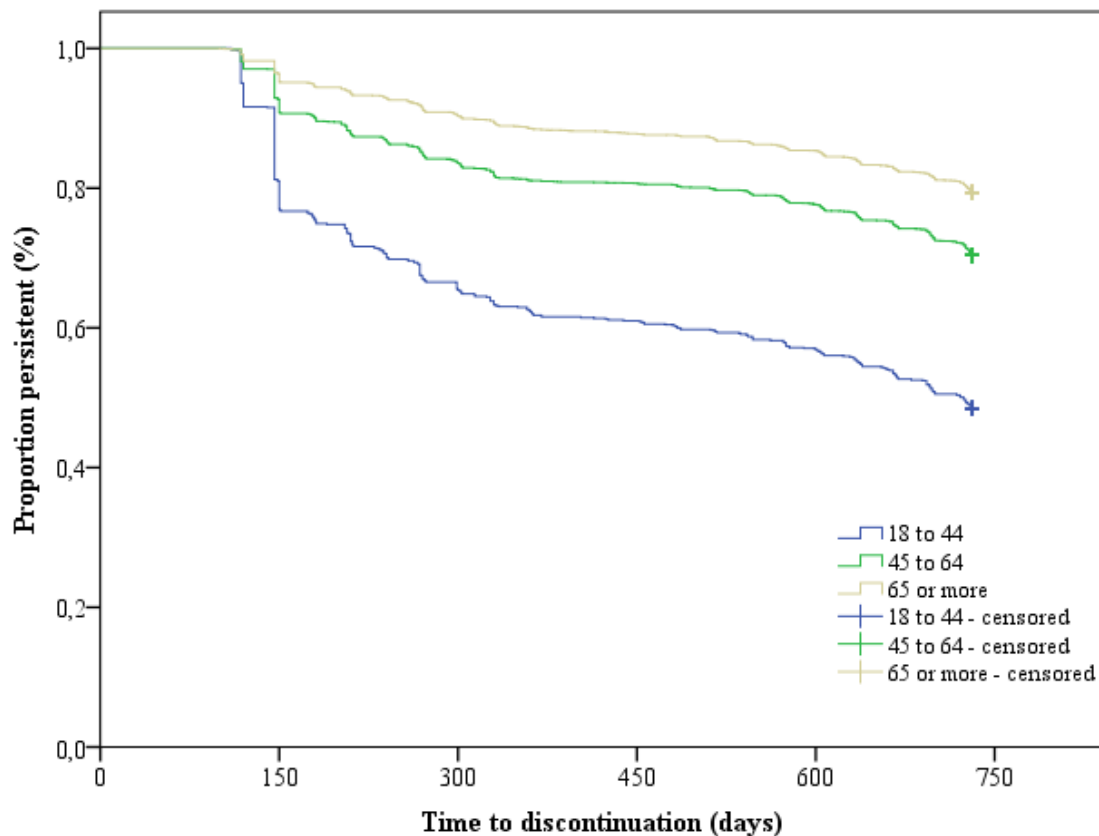
**Figure 21. Persistence, including reinitiation, to AHT therapy by age group**

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 – Antihypertensives; 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).
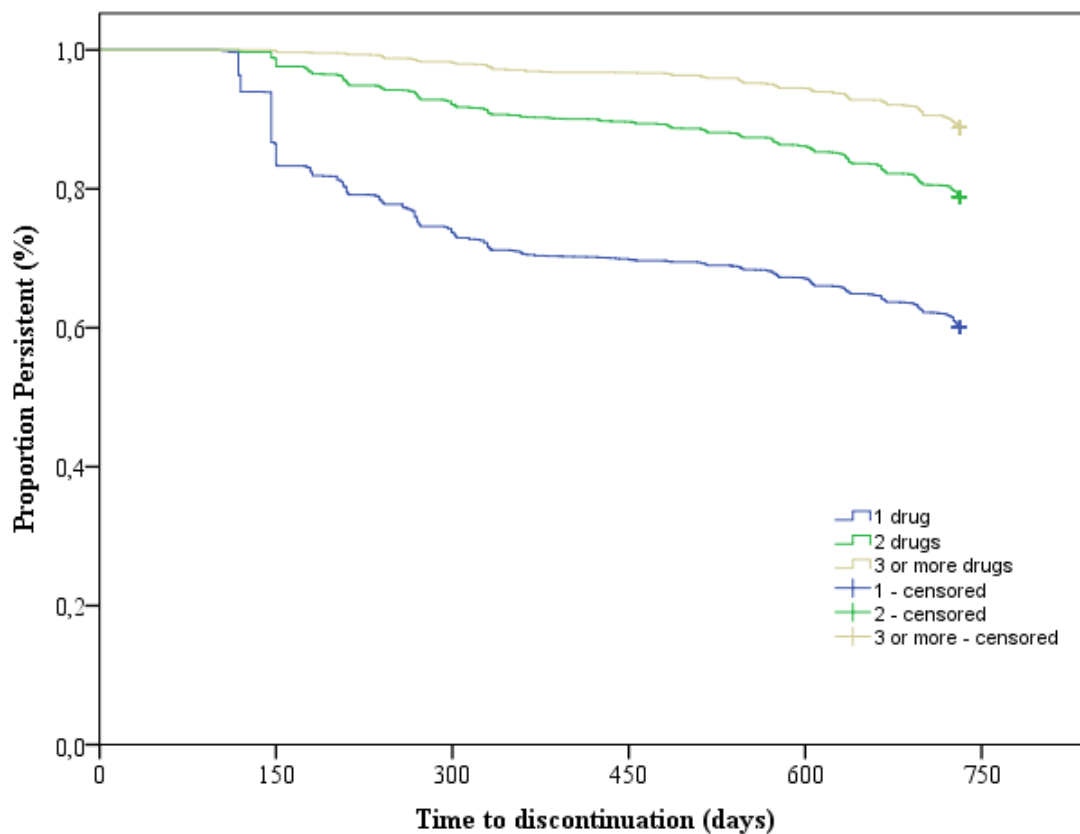
**Figure 22. Persistence, including reinitiation, to AHT therapy considering the number of dispensed drugs**

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

[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.