Representativeness of the "Fiesole Misurata"study database for use in pharmaco-epidemiological investigations on adherence to antihypertensive medications

Running head: Representativeness of the "Fiesole Misurata" study database

Francesco Lapi [1,2,3], Ersilia Lucenteforte [1,*], Martina Moschini [1], Roberto Bonaiuti [1], Marina Di Pirro [1], Alessandro Barchielli [4], Silvia Benemei [1], Maddalena Belladonna [5], Nicola Nesti [5], Raffaele Coppini [1], Margherita Taras [6], Alfredo Vannacci [1], Andrea Ungar [5], Alessandro Mugelli [1].

1. Department of Preclinical and Clinical Pharmacology, Centre for Molecular Medicine (CIMMBA), University of Florence, Italy
2. Centre for Clinical Epidemiology and Community Studies, Sir Mortimer B. Davis Jewish General Hospital, Montreal, Quebec, Canada
3. Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal Quebec, Canada
4. Department of Epidemiology, Local Health Authority n°10, Florence, Italy
5. Unit of Gerontology and Geriatrics, Department of Critical Care Medicine and Surgery, University of Florence and Azienda Ospedaliero-Universitaria Careggi, Florence, Italy
6. Fiesole Municipality, Fiesole (Florence), Italy

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Correspondence to: Ersilia Lucenteforte, ScD, PhD
Department of Preclinical and Clinical Pharmacology - Centre for Molecular Medicine (CIMMBA)
University of Florence
viale G. Pieraccini 6 - 50139 Florence, Italy
tel. 055 4271333; fax 055 4271280
e-mail: ersilia.lucenteforte@unifi.it

ABSTRACT

Background and Aims: Poor adherence to medications is a major health concern especially among older subjects. To plan future studies to improve adherence, an epidemiological study, called "Fiesole Misurata", was conducted. The aim of the present paper was to verify the representativeness of the database in evaluating the AntiHyperTensives (AHTs)-taking behaviour.

Methods: Demographic records of all subjects aged ≥ 65 years (n=2,228) living in the community of Fiesole (Florence, Italy) was retrieved from the Registry Office of Fiesole Municipality. The corresponding healthcare records were obtained from administrative archives of the Local Health Authority (claim dataset). Moreover, a cohort of subjects aged ≥65 years (n=385) living in the community was screened by means of a multidimensional geriatric evaluation (cross-sectional dataset).

Results: In claim dataset, biyearly prevalences of hospitalization for ischemic cardiomyopathy, heart failure, and stroke were 3.7%, 3.0%, and 3.2%, respectively. In the cross-sectional dataset, prevalences were 11.2%, 6.7%, and 7.1%, respectively. The most used drugs were angiotensin-converting enzyme (ACE) inhibitors (43.6% in the claim dataset, 45.3% in the cross-sectional dataset) and diuretics (35.6% and 47.0%, respectively). Among the incident users of AHTs, 63.5% was highly adherent (≥80%) over the first six months of follow-up, while 14.3% and 22.2% were intermediate (40-79%) and low (<40%) adherent. The percentage of high adherers decreased with time and reached 31.2% at the 24th month.

Conclusions: These findings indicate that "Fiesole Misurata" study database can be used to develop future strategies aimed at improving the adherence to AHTs in older individuals.

INTRODUCTION

Poor adherence to medications is a major health concern [1] especially among older subjects. Generally, when all drug categories are taken into account, the proportion of non-adherent older subjects varies from 40 to 75% [2]. This issue is particularly relevant for chronic asymptomatic diseases, such as hypertension, dyslipidaemias, diabetes,or other age-related disorders.

In specific, most of the fatal CardioVascular (CV) events occur in individuals aged 65 or older, in which the prevalence of hypertension is greater than in younger adults and leads to half and approximately to two-thirds of Coronary Heart Diseases (CHD), and cerebrovascular events, respectively [3-6]. Therefore, an inadequate Blood Pressure (BP) control could significantly increase the risk of death because of ischemic heart disease and stroke [7-9].

Although data on the clinical burden of non-adherence to AntiHyperTensives (AHTs) among older individuals are scanty, prior findings raised concerns about the relevance of non-adherence to AHTs, that hampers the effectiveness of these medications. Specifically, it has been demonstrated that among middle-aged patients an high adherence to AHTs is associated with a significant decreased risk (38%) of major CV events when compared with a low adherence [10].

The basis of poor medication-taking behaviour is multifactorial, as demonstrated by the strict relationship between a greater therapeutic complexity and a low adherence to CV medications [11]. In this context, the older community-dwelling people are the best example of therapeutic complexity, given the higher number of coexistent diseases and concomitant medications as well as the co-occurrence of other conditions, such as functional and cognitive impairments, age-related physiological complications (i.e.,

reduced liver and kidney function), which cannot be necessarily ascribed to a specific organic disease [12].

There are many unanswered questions on the most effective strategies for improving medications adherence in older subjects. They can be addressed with the use of electronic healthcare databases [13]. Claim repositories, which comprise all reimbursed drug prescriptions, hospital admissions diagnoses, and mortality registers can be valid tools in implementing intervention strategies. Nevertheless, claim databases are not designed for a specific research question, so certain variables (i.e. values of BP, disability and cognitive status) are often unavailable [2, 14]. For this reason, research on antihypertensive non-adherence in the elderly, cannot be exhaustively satisfied with the use of claim database since some confounders are not measurable.

To overcome this issue and with the aim to plan future studies to improve adherence, an epidemiological study, called the "Fiesole Misurata" study, was conducted in Fiesole, a small town of Tuscany, Italy, located in the hill north of Florence, and an *ad hoc* database was assembled. The name of the study can be translated as "Measuring Fiesole" since the database comprises several "measurements" (overall representing a multidimensional evaluation) of the population living in Fiesole, including socio-demographic and clinical information of all older (≥65 years) residents, who were retrospectively collected using claims data. In addition, a cohort of subjects underwent a multidimensional geriatric evaluation with the aim of estimating clinical variables (measures) which are generally unavailable in the administrative repositories.

As a first step, we verified the database representativeness in evaluating the AHTs-taking behaviour: to this aim, data of the "Fiesole Misurata" study concerning

CV diseases, pharmacotherapy and geriatric assessments were compared with those from other epidemiological studies and official statistics.

METHODS

The target population of the "Fiesole Misurata" study database was composed of individuals aged 65 or more living in Fiesole county (Tuscany, Italy). The community living in this area is distributed in nine districts (Fiesole City, Anchetta, Caldine, Compiobbi, Ellera, Girone, Pian del Mugnone, Pian di San Bartolo, San Domenico) and counts 14,264 inhabitants over an area of 42.11 km^2 (population density: 340,6 km^2). Fiesole citizens have the third highest mean income (€ 17,638 per resident) of Tuscany and the 51st of Italy [15].

Firstly, a list of all residents aged 65 years or more in the community of Fiesole was obtained on May 1st 2010 from the Municipality Registry Office and was merged with the healthcare records obtained from administrative archives of the Local Health Authority was performed by using the citizen's fiscal code as unique identifier (n=2,228, the claim dataset). Any identification code was automatically converted to a unique anonymous code [16].

Afterwards, all eligible subjects (n=2,228) were contacted by phone, were informed about the study, and were asked for their participation. Three-hundred and eighty-five subjects aged 65 years or more living in the community of Fiesole city decided to participate (n=385, the cross-sectional dataset). Therefore, an appointment was scheduled for each participant and data on multidimensional geriatric assessment (including BP measurement), self-reported drug consumption, and information on socio-demographic status along with lifestyle-related features were collected.

The study was approved by the Local Ethic Committee, and all participants signed their informed consent before being interviewed or visited.

Data collection

Claims dataset

Admission diagnoses (coded by the *International Classification Disease, 9th version, Clinical Modification* -ICD9CM) [17-21] and all reimbursed drug prescriptions (coded by the *Anatomical Therapeutic Chemical* -ATC- classification) were retrospectively obtained for the period between 1 January, 2008 and 31 July , 2010.

Hospital admissions (in primary and/or secondary positions) for diabetes (ICD9CM code or antidiabetics use, ATC A10*), ischemic cardiomyopathy, heart failure, haemorrhagic and ischemic stroke, cardiac arrhythmia, were identified.

All AHTs pharmacy claims related to Angiotensin-Converting Enzyme (ACE) inhibitors, angiotensin II receptor antagonist (sartans), diuretics, DiHydroPiridine (DHP) Calcium Channel Blockers (CCBs), non-DHP CCBs, beta blockers, peripheral alpha blockers, central inhibitors and the fixed combinations (i.e., ACE inhibitors or sartans or beta blockers with diuretics) were extracted. Furthermore, antithrombotics, antiarrhythmics, lipid lowering drugs and digitalis, as well as the number of ATC categories and hospitalizations being recorded for each elderly resident, were collected.

Cross-sectional dataset

Trained pharmacists interviewed all participants by means of a structured questionnaire on medications use (within the week which preceded the enrolment), socio-demographic information (i.e., years of education, marital status) and lifestyle habits

(i.e., nutrition, alcohol use and smoking), while six physicians (either geriatricians or clinical pharmacologists) performed the multidimensional assessment and measured the BP.

Disability was evaluated with both Instrumental and Basic Activities of Daily Living (IADL and BADL) [22]. Cognitive impairment, depressive or anxiety symptoms were assessed by the Mini Mental State Examination (MMSE) [23] and the Geriatric Depression Scale (GDS) [24].

Blood pressure was measured twice in each arm with the patients in the supine position, after having rested for at least 10 minutes in a quiet room at a comfortable temperature. A cuff larger than the standard was used when arm circumference exceeded 32 cm. The three sets of two BP measures were averaged, and the mean values were considered as the reference systolic and diastolic BP [25].

To evaluate Orthostatic Hypotension (OH), BP was also measured on standing from sitting or supine position according to a time interval of 1, 3 and 5 minutes of standing [26].

Finally, all subjects were required to report previous diagnoses they might have received from a pre-specified list of conditions by answering the question, '*'Has your doctor ever told you have…?''* [27]. All CV diseases being collected by means of claims data were purposely recollected together with asthma, chronic bronchitis, liver diseases, peptic ulcer and cancer [28].

Representativeness

To verify the representativeness of the "Fiesole Misurata" study database, the following estimates were computed:

- prevalence of CV diseases;
- prevalence of geriatric-related assessments, based on the standard cut-off points (i.e., BADL ≥1, MMSE≤21, GDS ≥6);
- distribution of co-morbidities (i.e., Silver Code scale) [28] and concomitant medications (i.e., count of ATC classes);
- prevalence of AHTs use among individuals with self-reported and diagnosed hypertension;
- distribution of adherence levels to AHTs.

Data analysis

Percentages, mean values, and related 95% Confidence Intervals (CIs) were computed for categorical and continuous variables,.

Proportions of socio-demographic, lifestyle and clinical features (i.e., geriatric assessments, comorbidity and overall medication use) were calculated by using the 2,228 residents and 385 survey participants as denominators for claims and cross-sectional dataset, respectively.

Blood pressure categories were defined by following the official guidelines [9, 29-31]. Subjects were diagnosed according to different thresholds, and classified as having ‘Optimal’ (<120/<80 mmHg), ‘Normal’ (120-129/80-84 mmHg), ‘High normal’ (130-139/80-85 mmHg), ‘Hypertension, grade I’ (140-149/90-99 mmHg), ‘Hypertension, grade II-III’ (>160/>100 mmHg), ‘Isolate systolic’ (>140/<90 mmHg) BP. The OH was defined as a decrease of at least 20 mm Hg in systolic BP (or systolic BP less than 90 mm Hg) or a decrease of at least 10 mm Hg in diastolic BP when changing from clinostatism to orthostatism [26].

Basic Activities of Daily Living and IADL were registered as continuous and categorical variables. The categorization was obtained by grouping subjects who had lost more than 1 functional autonomy against those who had not lost any of them. According to the literature, MMSE score, which decreases with cognitive impairment, and the GDS score, which increases with depression symptoms, were dichotomized at 21 [23] and 6 [24], respectively. The Silver Code was adopted to estimate to the burden of co-morbidity: as per Di Bari and co-workers [28] population was stratified into four prognostic groups based on the individual score (0–3, 4–6, 7–10, and ≥11).

With regard to medications, at first, the distribution of AHT classes and other CV medications were computed as proportional values in both claims and cross-sectional dataset. Consequently, using the claims data, Drug Daily Dosages (DDDs/1000 inhabitants/day) being prescribed for AHTs as a class and stratified by any single chemical group, were calculated over two years (1 May, 2008- 31 April, 2009 *versus* 1 May, 2009-31 April, 2010). Then, the degree of adherence to AHT was calculated, in claims dataset, among the incident users of AHT. As such, all subjects receiving the first prescription (cohort entry) of AHT from the 1st June 2008 to the 31st February 2010 were identified (i.e., excluding patients prescribed AHTs before the cohort entry). In addition, those with less than 180 days of follow-up after the first prescription were excluded. The adherence was computed as Proportion of Days Covered (PDC), calculated by dividing the cumulative days of AHTs use by the length of follow-up. The number of days supplied from each prescription was calculated by dividing the total amount of active drug in each prescription by the recommended DDDs. All dispensed prescriptions were considered interchangeable. Thus, all overlaps between two or more AHTs prescriptions were subtracted by the total cumulative days

of use. When a gap between two treatment periods was ≤90 days, subjects were still considered being on therapy. Therefore, progressively growing adherence was categorized as low with a PDC value <40% , intermediate and high with PDC values 40-79% and ≥80%, respectively [10, 32]. According to the subject-specific follow-up, PDC strata were computed at intervals of 6, 12, 18 and 24 months.

Finally, subjects who had at least two prescriptions of AHTs, according to their self-reported and diagnosed hypertension, were categorized as 'self-reported', 'mild-degree' (130-139/81-89 mmHg)' and 'severe-degree' (≥140/≥90 mmHg) hypertensive subjects.

RESULTS

The claim and cross-sectional dataset consisted of 2,228 and 385 older individuals, respectively. In both datasets, most individuals were females. In the claim dataset, the highest proportion of subjects were less than 70 years, in the cross-sectional dataset the highest proportion of subjects were 70-74 years (**Table 1**). In the claim dataset, females were older than males, while in the cross-sectional one, age categories were equally distributed between genders.

Drugs were purchased in 269 different pharmacies, but three of them covered 84% of all dispensed medications. Moreover, patients were assisted by a total of 128 general practitioners with eight of them covering 82% of them.

In the claim dataset, the burden of comorbidity was lower in females then in males, especially for the highest sub-category of the Silver Code (8.4% *versus* 15.3%,

Table 2). These results were in line with the number of hospitalizations per subject, the number of concomitant medications and the prevalence of hospitalizations due to CV diseases. Among the latters, ischemic cardiomyopathy was 3-fold higher in males than in females, and the corresponding CIs were not overlapped. This picture was maintained among AHTs users, where males outnumbered females for any medication class with the exception of diuretics, central inhibitors and fixed combinations (**Table 3**).

As a whole, the prescribed DDDs were higher in 2009 as compared to 2008 for all AHTs, with the exception of ACE inhibitors (**Figure 1**).

Two-hundred-and-thirty individuals (10.3%of 2,228) constituted the AHT inception dataset. In detail 63.5% were highly adherent to AHTs over the first six months of their treatment, while 14.3% and 22.2% showed intermediate and low levels, respectively (**Figure 2**). The percentage of the high adherent subjects decreased with time reaching 31.2% at the 24^{th} month.

The prevalence of self-reported and diagnosed hypertension was lower in females than in males (**Table 4**). In contrast, OH was more frequent among females. Subjects who had BP equal to or over than 140/90 mmHg underreported to suffer from hypertension. Specifically, 36/86 (41.9%) females and 28/68 (41.2%) males wrongly reported to be normotensive or mild-hypertensive, respectively (**data not shown**). With the exception of dyslipidaemia, all CV diseases appeared more common in males, as well as the reduction of cognitive functions (**Table 4**). On the contrary, females were more functionally impaired and more depressed than men. Taken as whole, disability, cognitive status and depression degree accordingly increased with the participants' age.

The prevalent users of AHTs were slightly higher among females, almost for all medication classes. Only sartans and peripheral alpha blockers were more frequently

prescribed in males (**Table 5**). Diuretics were the most reported medications, followed by ACE inhibitors and sartans (47.0%, 45.3%, and 33.6%, respectively).

Generally, almost the 70% of subjects with clinically assessed mild or severe hypertension were pharmacologically treated (**Figure 3**).

DISCUSSION

This paper describes the methodology with which the representativeness of the "Fiesole Misurata" database was evaluated. To our knowledge, this is the first pharmaco-epidemiological tool focused on older subjects which comprises both administrative and clinical information.

In the claim dataset, the distribution of age categories was acceptably representative of the Italian older population, although the prevalence of older people was slightly lower than that reported by the official statistics (16% in Fiesole *versus* 18-20% in Italy) [15, 33], and about 25% aged more than 80 years. Concerning the cross-sectional dataset, the lower number of younger participants was likely due to self-selection of subjects after the proposal of participation.. Indeed, the fact that subjects were instructed about the study topic could have fostered the participation of elders aged more than 70, who knew better their CV conditions and were featured by an higher burden of comorbidity [18, 27, 28, 34].

Also the prevalence of CV diseases was in line with previous results. As shown by "Progetto Cuore" (a comprehensive study on epidemiology of CV diseases in Italy) [8, 35, 36], and in keeping with what was found in other international contexts [3, 5, 6], these diseases are more common in males. On the other hand, the comparison between claim and cross-sectional dataset showed some differences. The fact that acute events

(i.e., ischemic cardiomyopathy, stroke, certain arrhythmias) were more frequently reported in the cross-sectional dataset is likely due to the cumulative effect of the self-reported diagnoses. In fact, while they can cover the entire life-time period of each participant, the clinical history in claim datasets was limited to the previous two-year period. , Consistently, our cross-sectional estimates agreed with those obtained by Landi and coworkers [18] who enrolled patients with a similar design Also heart failure was more prevalent in the cross-sectional dataset. The discrepancy with claim dataset is likely due to the aforementioned reasons along with the chronic course of this disease [37]. In fact, hospitalizations due to exacerbations of heart failure could occur in a period longer than that we were able to analyse.

According to "Fiesole Misurata" study, 27.0% of subjects were classified as functionally impaired. These estimates were in keeping with similar surveys [38, 39]. Accordingly, the prevalence of cognitive status [40], depression [41], OH [26], burden of comorbidities [18, 34] and co-medications [18, 42-45] were consistent with previous estimates.

As hypertension was considered, the self-reporting diagnoses underestimated (almost 10% lower) the prevalence of hypertension when compared with the actual BP measurement during the study. Specifically, more than one-third of participants misclassified their BP status; this is in line with the fact that elderly individuals usually underestimate their levels of BP, even if patients' unawareness of hypertension is recently decreased in western countries [29]. Furthermore, while the percentage of subjects with severe hypertension was higher than 65%, the adherence to AHTs sensibly decreased during the two years after the first prescription. In any case, more than 20% of individuals with severe hypertension did not receive any prescription, and more than

30% of the incident users were non-adherent in the first six months of follow-up. These findings demonstrate that the poor AHTs-taking behaviour is quantitatively similar to that reported in the middle-aged population [10, 32]. These results were further strengthened by the fact that the prevalence of each single drug category and the prescribed DDDs agreed with the official prescription reports [46, 47] and previous investigations [48].

From a public health perspective, the "Fiesole Misurata" study could be important in several ways. First of all, it offers a comprehensive picture of a community-based older population in terms of health claim information and clinical features. Furthermore, the quantification of AHTs non-adherence, as well as the measurement of OH, have not been previously reported in an Italian elderly population.

Certainly, the present study has limitations. Firstly, the cross-sectional sample has not been randomly selected and it could be therefore affected by selection bias. However, given that all estimates concerning both diseases and medications use were consistent with prior studies, the driven selection of certain patients' categories should have been minimized. Secondly, some diagnoses coded in claims databases could be underestimated because they are limited to hospital discharge charts. Nevertheless, given that elders are more frequently hospitalized than younger adults, we can assume that underestimation of cardiovascular and other specific diseases (e.g., COPD) is generally negligible in this age category. Finally, claims databases do not comprise the indication of drug use. As a consequence, subjects cannot be differentiated between those who suffer from hypertension and/or heart failure or other conditions. However, the non-adherent behaviour to AHTs equally affects all CV illnesses.

Despite these limitations, the present study does not undermine the observed values, particularly considering few Randomized Clinical Trials (RCTs) are conducted in elderly patients, and RCTs often fail to appropriately evaluate the issues related to medications-non-adherence [2]. In particular, differences in drug tolerability, dosing variability, and patient perceptions of the disease are observational (i.e., "real-world") variables which can remarkably influence the adherence to AHTs. For this reason, appropriate strategies to correct these factors should be implemented.

Given that the clinical characteristics of older people residents in Fiesole appear consistent with those of the Italian older population, it is our opinion that further strategies aimed at improving the adherence to AHTs can be implemented and epidemiologically verified by adopting "Fiesole Misurata" study database.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Figure Legends

Figure 1. Use of antihypertensives broken down by the period of use in the claim dataset (DDD/1000 inhabitants/die). ACE: Angiotensin-Converting Enzyme; CCBs : Calcium Channel Blockers; DDDs: Drug Daily Dosages

Figure 2. Degree of adherence among new users of antihypertensives in the AHT dataset. AHT: AntiHyperTensive

Figure 3. Degree of treatment among self-reported and diagnosed hypertensive subjects in the cross-sectional dataset. Mild hypertensive subjects: blood pressure 130-139/81-89 mmHg; Severe hypertensive subjects: blood pressure ≥140/≥90 mmHg; Treated: at least two antihypertensive prescriptions.

Figure 1. Use of antihypertensives broken down by the period of use in the claim dataset (DDD/1000 inhabitants/die). ACE: Angiotensin-Converting Enzyme; CCBs : Calcium Channel Blockers; DDDs: Drug Daily Dosages

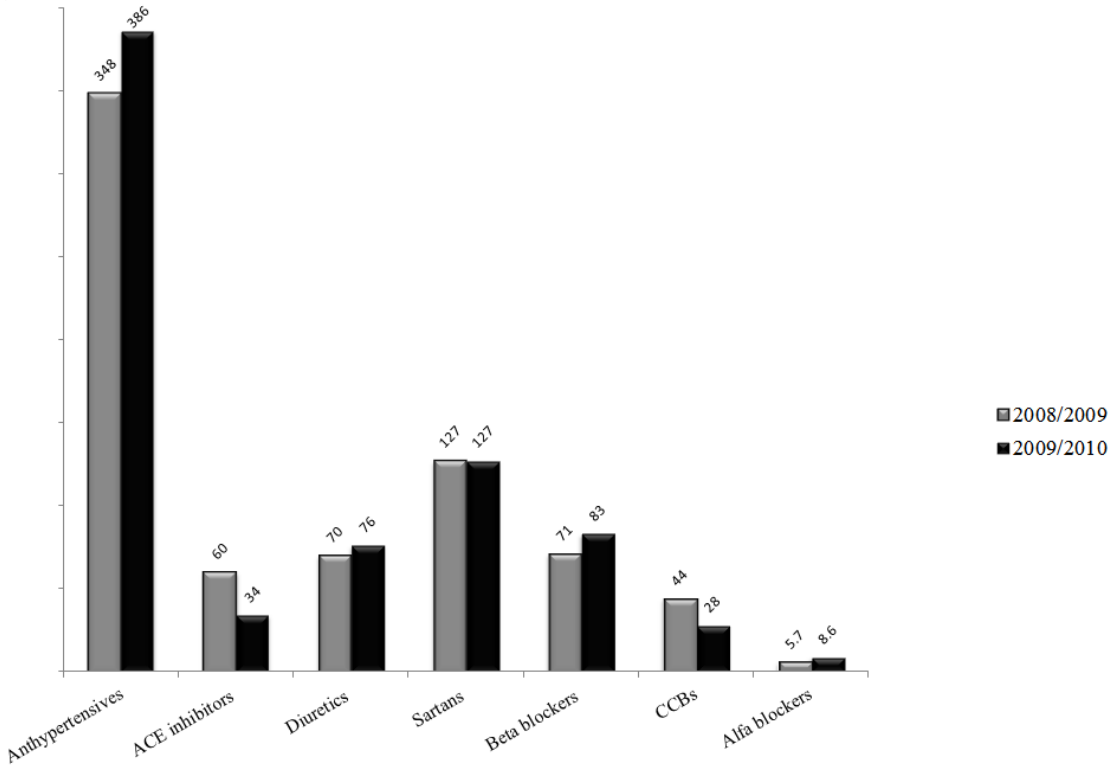

Figure 2. Degree of adherence among new users of antihypertensives in the AHT dataset. AHT: AntiHyperTensive

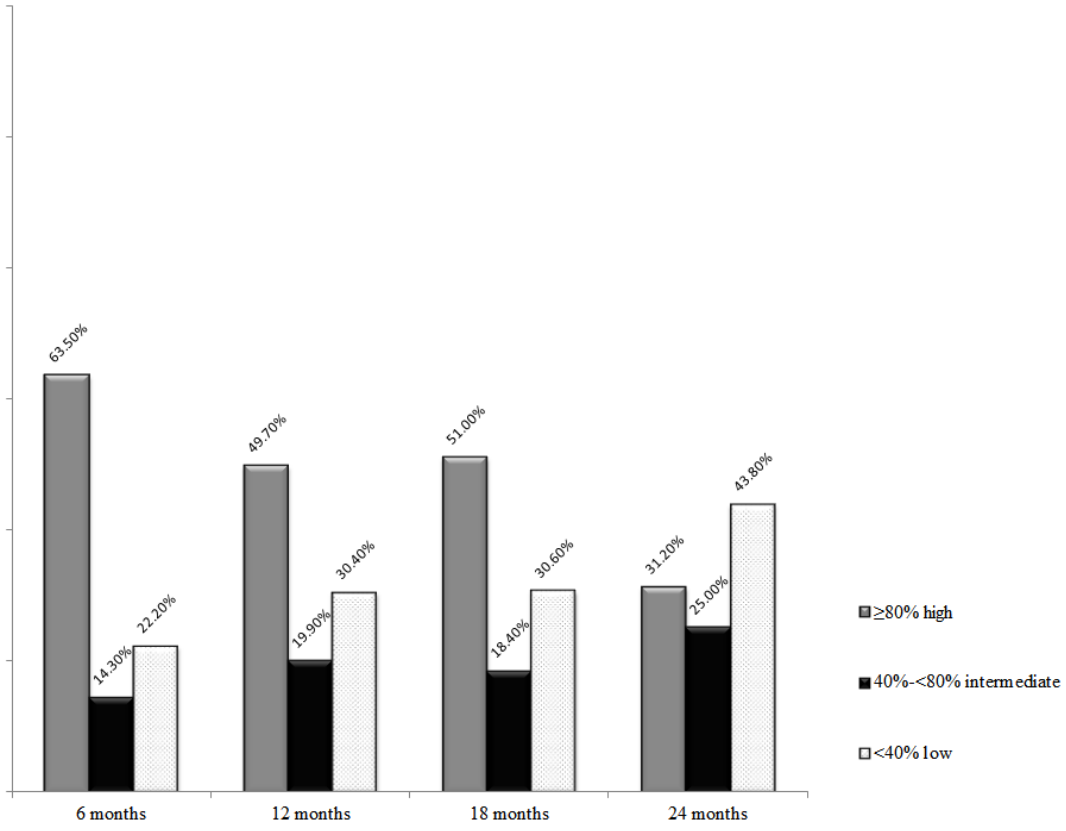

Figure 3. Degree of treatment among self-reported and diagnosed hypertensive subjects in the cross-sectional dataset. Mild hypertensive subjects: blood pressure 130-139/81-89 mmHg; Severe hypertensive subjects: blood pressure ≥140/≥90 mmHg; Treated: at least two antihypertensive prescriptions.

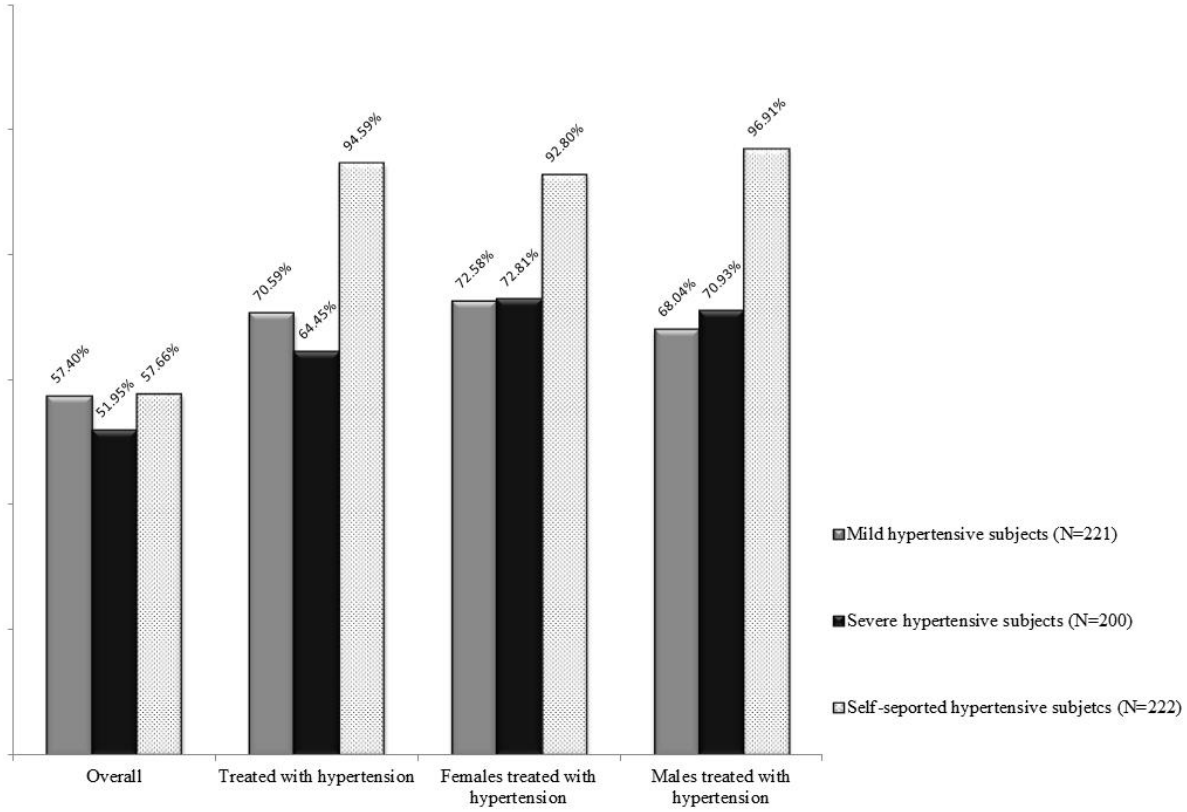

Table 1. Distribution of older subjects' demographics in the claim (n=2,228) and the cross-sectional (n=385) dataset.

	Number Percentage (95% CI)		
	Overall	**Females**	**Males**
Claims dataset			
No. of residents	2,228	1,274	954
Age (years)			
<70	743 33.4 (31.4-35.3)	395 31.0 (28.4-33.6)	348 36.4 (33.4-39.6)
70-74	515 23.1 (21.4-24.9)	295 23.2 (20.9-25.6)	220 23.1 (20.4-25.9)
75-79	413 18.5 (16.9-20.2)	226 17.7 (15.7-19.9)	187 19.6 (17.1-22.2)
80-84	308 13.8 (12.4-15-3)	186 14.6 (12.7-16.6)	122 12.8 (10.7-15.1)
>84	249 11.2 (9.9-12.6)	172 13.5 (11.7-15.5)	77 8.1 (6.4-10.0)
Cross-sectional dataset			
No. of participants	385	220	165
Age (years)			
<70	76 19.7 (15.9-2.1)	41 18.6 (13.7-24.4)	35 21.2 (15.2-28.2)
70-74	92 23.9 (19.1-28.5)	63 28.7 (22.8-35.1)	29 17.6 (12.1-24.3)
75-79	83 21.6 (17.6-26.0)	46 20.9 (15.7-26.9)	37 22.4 (16.3-29.6)
80-84	74 19.2 (15.4-23.5)	39 17.7 (12.9-23.4)	35 21.2 (15.2-28.2)
>84	60 15.6 (12.1-19.6)	31 14.1 (9.8-19.4)	29 17.6 (12.1-24.3)

Table 2. Distribution of residents' clinical features in the claims dataset (n=2,228).

	Number Percentage (95% CI)		
	Overall (N=2,228)	**Females (N=1,274)**	**Males (N=954)**
Silver Code categories			
0-3	1,459 65.5 (63.4-67.4)	912 71.6 (68.9-74.0)	547 57.3 (54.1-60.5)
4-6	364 16.3 (14.9-18.0)	138 10.8 (9.2-12.7)	226 23.7 (21.0-26.5)
7-10	152 6.8 (5.8-7.9)	117 9.2 (7.6-10.9)	35 3.7 (2.6-5.1)
≥11	253 11.4 (10.1-12.7)	107 8.4 (6.9-10.0)	146 15.3 (13.1-17.7)
Hospitalizations/Subjects [a]	1,271/2,228 0.6	653/1,274 0.5	618/954 0.6
Number of subjects with hospital data	663 29.8 (27.9-31.7)	342 26.8 (24.4-29.4)	321 33.6 (30.6-36.4)
Prevalent hospitalizations			
Diabetes (or antidiabetics: ATC A10*)	313 14.0 (12.6-15.6)	152 11.9 (10.2-13.8)	161 16.7 (14.5-1.94)
Ischemic cardiomyopathy	83 3.7 (3.0-4.6)	26 2.0 (1.3-3.0)	57 6.0 (4.6-7.7)
Heart failure	67 3.0 (2.3-3.8)	33 2.6 (1.8-3.6)	34 3.6 (2.5-4.9)
Haemorrhagic and ischemic stroke	72 3.2 (2.5-4.0)	38 3.0 (2.1-4.1)	34 3.6 (2.5-4.9)
Cardiac Arrhythmia	77 3.5 (2.7-4.3)	37 2.9 (2.1-4.0)	40 4.2 (3.0-5.7)
Number of co-prescribed drugs [b]			
mean (±SD)	5.2 (± 5.1)	5.8 (± 4.6)	5.6 (± 5.5)
Number of medications			
0	1,377 61.8 (59.7-63.8)	824 64.7 (62.0-67.3)	553 58.0 (54.8-61.1)
1-4	578 26.0 (24.1-27.8)	320 25.1 (22.7-27.6)	258 27.0 (24.2-30.0)
≥5	273 12.2 (10.9-13.7)	130 10.2 (8.6-12.0)	143 15.0 (12.8-17.4)

[a] ratio

[b] any single ATC among medication users

Table 3. Distribution of resident's use of antihypertensives and other CV medications in the claim dataset (n=2,228).

	Number Percentage (95% CI)		
	Overall (N=2,228)	**Females (N=1,274)**	**Males (N=954)**
Prevalent users of antihypertensives [a]			
Overall	1,507 67.6 (65.6-69.6)	869 68.2 (65.6-70.8)	638 66.9 (63.8-69.8)
Age strata (years)			
<70	743 54.2 (50.6-57.9)	395 54.2 (49.1-59.2)	348 54.3 (48.9-59.6)
70-74	515 68.3 (64.1-72.3)	295 65.1 (59.3-70.5)	220 72.7 (66.3-78.5)
75-79	413 74.8 (70.3-78.9)	226 76.1 (70.0-81.5)	187 73.3 (66.3-79.5)
80-84	308 76.9 (71.8-81.5)	186 80.6 (74.2-86.1)	122 71.3 (62.4-79.1)
>84	249 82.7 (77.4-87.2)	172 82.0 (75.4-87.4)	77 84.4 (74.4-91.7)
Medication class [a]			
ACE inhibitors (C09A*)	657 43.6 (41.1-46.1)	352 40.5 (37.2-43.8)	305 47.8 (43.9-51.8)
Diuretics (C03*)	536 35.6 (33.1-38.0)	324 37.3 (34.0-40.6)	212 33.2 (29.6-37.0)
Sartans (C09C*)	371 24.6 (22.5-26.9)	204 23.5 (20.7-26.4)	167 26.2 (22.8-29.8)
Beta blockers (C07A*; C07EA*)	454 30.1 (27.8-32.5)	248 28.5 (25.5-31.7)	206 32.3 (28.7-36.1)
CCBs – DHP (C08CA*)	482 32.0 (29.6-34.4)	271 31.2 (28.1-34.4)	211 33.1 (29.4-36.9)
Central inhibitors (C02A*)	26 1.7 (1.1-2.5)	16 1.8 (1.0-3.0)	10 1.6 (0.7-2.9)
Alfa blockers, peripheral (C02C*)	148 9.8 (8.4-11.4)	59 6.8 (5.2-8.7)	89 13.9 (11.3-16.9)
CCBs - non DHP (C08CX01; C08D*; C08E*)	100 6.6 (5.4-8.0)	51 5.9 (4.4-7.6)	49 7.7 (5.7-10.0)
Beta blockers and diuretics (C07B*; C07C)	30 2.0 (1.3-2.8)	20 2.3 (1.4-3.5)	10 1.6 (0.7-2.8)
ACE inhibitors and Diuretics (C09B*)	408 27.1 (24.8-29.4)	238 27.4 (24.4-30.5)	170 26.7 (23.2-30.2)
Diuretics and Sartans	342 22.7 (20.6-24.9)	210 24.2 (21.3-27.1)	132 20.7 (17.6-24.0)

Table 3. continues

Table 3. continued

	Number Percentage (95% CI)		
	Overall (N=2,228)	**Females (N=1,274)**	**Males (N=954)**
Prevalent users of other CV medications			
Antithrombotics (B01A*)	1134 50.9 (48.8-53.0)	611 48.0 (45.2-50.7)	523 54.8 (51.7-58.0)
Antiarrhythmics (C01B*)	636 28.5 (26.7-30.4)	336 26.4 (24.0-28.8)	300 31.4 (28.5-34.4)
Digitalis (C01A*)	131 5.9 (4.9-6.9)	66 5.2 (4.0-6.4)	65 6.8 (5.2-8.4)
Lipid lowering (C10*)	540 24.2 (22.5-26.0)	270 21.2 (18.9-23.4)	270 28.3 (25.4-31.2)

ACE: Angiotensin-Converting Enzyme
CV: CardioVascular
CCBs : Calcium Channel Blockers
DHP: dihydropiridinic
[a] denominator: prevalent users of antihypertensive medications (n=1,507)

Table 4. Distribution of subject's clinical features in the cross-sectional dataset (n=385).

	Number Percentage (95% CI)		
	Overall (N=385)	**Females (N=220)**	**Males (N=165)**
BP (mmHg)			
Optimal: <120/<80	71 18.4 (14.7-22.7)	43 19.5 (14.5-25.4)	28 17.0 (11.6-23.6)
Normal: 120-129/80-84	114 29.6 (25.1-34.4)	69 31.4 (25.3-37.9)	45 27.3 (20.6-34.7)
High normal: 130-139/80-85	32 8.3 (5.7-11.5)	16 7.3 (4.2-11.5)	16 9.7 (5.6-15.3)
Hypertension, grade I: 140-159/90-99	43 11.2 (8.2-14.7)	22 10.0 (6.3-14.7)	21 12.7 (8.0-18.8)
Hypertension, grade II-III: >160/>100	23 6.0 (3.8-8.8)	13 5.9 (3.2-9.9)	10 6.1 (2.9-10.9)
Isolate Systolic: >140/<90	88 22.9 (18.8-27.4)	51 23.2 (17.8-29.3)	37 22.4 (16.3-29.6)
missing	*14* *3.6 (0.2-6.0)*	*6* *2.7 (0.1-5.8)*	*8* *4.8 (2.1-9.3)*
Orthostatic Hypotension [a]			
No	306 79.5 (75.1-85.3)	174 79.1 (73.1-84.3)	132 80.0 (73.1-85.8)
Yes	48 12.5 (9.3-16.2)	31 14.1 (9.8-19.4)	17 10.3 (6.1-16.0)
missing	*31* *8.0 (5.5-11.2)*	*15* *6.8 (3.8-11.0)*	*16* *9.7 (5.6-15.3)*
Cardiovascular disease			
Dyslipidaemia	141 36.6 (31.8-41.6)	96 43.6 (37.0-50.2)	45 27.3 (20.4-34.1)
Diabetes (or use of antidiabetic drugs)	52 13.5 (10.1-16.9)	28 12.7 (8.3-17.2)	24 14.5 (9.1-20.0)
Ischemic cardiomyopathy	43 11.2 (8.0-14.3)	20 9.1 (5.3-12.9)	23 13.9 (8.6-19.3)
Heart failure	26 6.7 (4.2-9.3)	14 6.4 (3.1-9.6)	12 7.3 (3.3-11.3)
Haemorrhagic and ischemic stroke	27 7.1 (4.4-9.6)	15 6.8 (3.5-10.2)	12 7.3 (3.3-11.3)
Self-reported hypertension	222 57.7 (52.7-62.6)	125 56.8 (50.2-63.4)	97 58.8 (51.2-66.4)

Table 4. continues

Table 4. continued

	Number Percentage (95% CI)		
	Overall (N=385)	**Females (N=220)**	**Males (N=165)**
Functional status (lost)			
BADL, mean (± SD)	0.6 (±1.3) (0.5-0.7)	0.6 (±1.4) (0.5-0.8)	0.5 (±1.3) (0.3-0.7)
IADL, mean (± SD)	0.7 (±1.7) (0.5-0.8)	0.8 (±1.8) (0.5-1.0)	0.5 (±1.5) (0.3-0.8)
BADL ≥1			
Overall	104 27.0 (22.6-31.7)	66 30.0 (24.0-36.5)	38 23.0 (16.8-30.2)
Age strata			
<70	3 4.1 (0.9-11.5)	2 5.3 (0.6-17.7)	1 2.9 (0.7-14.9)
70-74	22 24.2 (15.8-34.3)	15 23.8 (14.0-36.2)	7 25.0 (10.7-44.9)
75-79	26 31.3 (21.6-42.4)	17 37.0 (23.2-52.4)	9 24.3 (11.8-41.2)
80-84	25 34.2 (23.5-46.3)	16 41.0 (25.6-57.9)	9 26.9 (12.9-44.4)
>84	28 53.8 (39.5-67.8)	16 57.1 (37.2-75.5)	12 50.0 (29.1-70.9)
missing	*13* *3.4 (1.8-5.7)*	*6* *2.7 (1.0-5.8)*	*7* *4.2 (1.7-8.5)*
Cognitive status			
MMSE, mean (± SD)	26.6 (±3.6) (26.3-27.0)	26.7 (±3.6) (26.2-27.2)	26.6 (±3.6) (26.0-27.2)
MMSE ≤21			
Overall	27 7.0 (4.7-10.0)	11 5.0 (2.5-8.8)	16 9.7 (5.6-15.3)
Age strata			
<70	1 1.3 (0.03-7.3)	1 2.6 (0.07-13.5)	-
70-74	2 2.2 (0.3-7.9)	1 1.6 (0.04-8.8)	1 3.6 (0.09-18.3)
75-79	3 3.6 (0.7-10.2)	3 6.5 (1.4-17.9)	-
80-84	4 5.4 (1.5-13.3)	1 2.6 (0.07-13.5)	3 8.6 (1.8-23.0)
>84	17 30.9 (19.1-44.8)	5 17.9 (6.1-36.9)	12 44.4 (25.5-64.7)
missing	*10* *2.6 (1.2-4.7)*	*7* *3.2 (1.3-6.4)*	*3* *1.8 (0.4-5.2)*

Table 4. continues

Table 4. continued

	Number Percentage (95% CI)		
	Overall (N=385)	**Females (N=220)**	**Males (N=165)**
Depression			
GDS, mean (± SD)	3.3 (±2.8) (3.0-3.6)	3.9 (±2.9) (3.5-4.3)	2.5 (±2.5) (2.1-2.9)
GDS ≥6			
Overall	77 20.0 (16.1-24.3)	54 24.5 (19.0-30.8)	23 13.9 (9.0-20.2)
Age strata			
<70	5 6.8 (2.2-15.1)	4 10.3 (2.9-24.2)	1 2.9 (0.07-14.9)
70-74	21 23.6 (15.2-33.8)	15 24.6 (14.5-37.3)	6 21.4 (8.3-40.9)
75-79	18 21.7 (13.4-32.1)	12 26.1 (14.3-41.1)	6 16.2 (6.2-32.0)
80-84	17 23.3 (14.2-34.6)	12 31.6 (17.5-48.6)	5 14.3 (4.8-30.3)
>84	16 30.8 (18.7-45.1)	11 42.3 (23.3-63.1)	5 19.2 (6.5-39.3)
missing	*14* *3.6 (2.0-6.0)*	*10* *4.5(2.2-8.2)*	*4* *2.4 (0.7-6.1)*

BADL: Basic Activity of Daily Living
BP: Blood Pressure
GDS: Geriatric Depression Scale
IADL: Instrumental Activity of Daily Living
MMSE: Mini Mental State Examination
SD: standard deviation
[a] defined as a decrease of at least 20 mm Hg in systolic BP (or systolic BP less than 90 mm Hg) or a decrease of at least 10 mm Hg in diastolic BP when changing from clinostatism to orthostatism.

Table 5. Distribution of subjects' use of antihypertensives in the cross-sectional dataset (n=385).

	Number Percentage (95% CI)		
	Overall (N=385)	**Females (N=220)**	**Males (N=165)**
Prevalent users of antihypertensives [a]			
Overall	247 64.2 (59.1-68.9)	143 65.0 (58.3-71.3)	104 63.0 (55.2-70.4)
Age strata (years)			
<70	41 54.0 (42.1-65.4)	23 56.1 (39.7-71.5)	18 51.4 (34.0-68.6)
70-74	55 59.8 (49.0-69.9)	35 55.6 (42.5-68.1)	20 69.0 (49.2-84.7)
75-79	59 71.1 (60.1-80.5)	31 67.4 (52.0-80.5)	28 75.7 (58.8-88.2)
80-84	52 70.3 (58.5-80.3)	28 71.8 (55.1-85.0)	24 68.6 (50.7-83.1)
>84	40 66.7 (53.3-78.3)	26 83.9 (66.3-94.5)	14 48.3 (29.4-67.5)
Medication class [a]			
ACE inhibitors	112 45.3 (39.0-51.8)	66 46.1 (37.8-54.7)	46 44.2 (34.5-54.3)
Diuretics	116 47.0 (40.6-53.4)	69 48.2 (39.8-56.7)	47 45.2 (35.4-55.2)
Sartans	83 33.6 (27.7-39.9)	46 32.2 (24.6-40.5)	37 35.6 (26.4-45.6)
Beta blockers	62 25.1 (19.8-31.0)	43 30.1 (22.7-38.2)	19 18.3 (11.4-27.0)
CCBs - DHP	51 20.7 (15.8-26.2)	32 22.4 (15.8-30.1)	19 18.3 (11.4-27.0)
Central inhibitors	45 18.2 (13.6-23.6)	33 23.1 (16.4-30.8)	12 11.5 (6.1-19.3)
Alfa blockers, peripheral	35 14.2 (10.1-19.1)	8 5.6 (2.4-10.7)	27 26.0 (17.9-25.5)
CCBs - non DHP	7 2.8 (1.1-5.7)	5 3.5 (1.1-8.0)	2 1.9 (0.2-6.8)
Prevalent users of other CV medications			
Antiaggregants	130 33.8 (29.0-38.7)	72 32.7 (26.6-39.4)	58 35.1 (27.9-43.0)
Statins	79 20.5 (16.6-24.9)	53 24.1 (10.6-30.3)	26 17.8 (10.6-22-2)

ACE: Angiotensin-Converting Enzyme
CV: CardioVascular
CCBs : Calcium Channel Blockers
DHP: dihydropiridinic
[a] denominator: prevalent users of antihypertensive medications (n=247)