Exploring factors associated with patients' adherence to antihypertensive drugs among people with primary hypertension in the United Kingdom

Short title: "Adherence and patients' characteristics"

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Abstract (248 words)

Objective

To explore factors associated with adherence to antihypertensive drugs overall ("therapy adherence") and to particular classes ("class adherence") in hypertensive patients.

Methods

This retrospective cohort study included adults with primary hypertension identified in the UK Clinical Practice Research Datalink from April/2006 to March/2013. Individuals were followed from the date of first-ever antihypertensive drug class (class adherence) prescribed and from the date of the first-ever antihypertensive drug (therapy adherence) issued to the earliest of study end, patient leaving the database or death. Prescribing episodes (time from a drug class being first prescribed to the end of follow-up time) of six antihypertensive drug classes were recorded. Proportion of Days Covered (PDC) was used to estimate therapeutic adherence for a patient's antihypertensive drugs therapy during follow-up period and class adherence of a specific antihypertensive class in each episode, respectively. Generalized linear modelling was used to examine factors associated with PDC.

Results

Median therapy and class PDC were 93.9% and 98.3% in the 176,835 patients and 371,605 prescribing episodes; 20% and 38.4% of the patients and episodes had PDC<80%, respectively. Higher therapy and class PDC was associated with increasing age, using renin angiotensin drugs and being pre-existing patient and user of antihypertensive drugs. Higher deprivation, multiple comorbidities and switching of antihypertensive drugs were associated with lower PDC.

Conclusions

Several patient factors were confirmed as determinant of adherence to antihypertensive drug classes and therapy; hence they can assist in identifying patients at risks of non-adherence; thus targeting them for adherence improving interventions.

Keywords

Adherence; Antihypertensive drugs; Clinical Practice Research Datalink; Generalized Linear model

List of Abbreviations

95%CI	95% Confidence Interval
ACEIs	Angiotensin-Converting Enzyme Inhibitors
ARBs	Angiotensin Receptor Blockers
BBs	Beta-Blockers
BP	Blood Pressure
CCBs	Calcium-Channel Blockers
CCI	Charlson Comorbidity Index
CPRD	Clinical Practice Research Datalink
CVDs	Cardiovascular Diseases
GLM	Generalised Linear Model
HT	Hypertension
IQR	Interquartile Range
MPR	Medication Possession Ratio
OLS	Ordinary Least Square
PDC	Proportion of Days Covered
SD	Standard Deviation
SES	Socio-Economic Status
UK	United Kingdom

Introduction

Hypertension (HT) is a highly prevalent condition in the United Kingdom (UK) with an estimated prevalence of 13.7% [1]. Antihypertensive drugs have been shown to reduce the risk of cardiovascular complications, premature mortality [2] and achieve cost-savings [3] in people with HT. Nevertheless, suboptimal control of BP has been consistently reported in population-based surveys of hypertension management worldwide [4, 5] .

Patients' poor adherence to antihypertensive drugs is considered one of the key contributing factors to suboptimal BP control [6]. Long-term adherence to antihypertensive therapy is crucial to achieve and maintain optimal BP control [7]. Reported adherence to antihypertensive drugs varies from 28% to 78% [8, 9], attributed mostly to differences in study populations, types of medications being considered, study designs, follow-up time, and definitions and measurement of adherence.

Poor adherence to antihypertensive drugs is associated with increased cardiovascular events and hospitalisations with subsequently high costs and healthcare resources utilisation [10, 11]. In England, the estimated potential cost of the health gains foregone as a result of non-adherence to antihypertensive drugs is about £390 million per annum [12]. It was also estimated that over £100 million per annum would be saved if 80% of people with hypertension were adherent to their medications [12].

Understanding factors associated with adherence is crucial for patients, and healthcare professionals and providers. Previous studies have found associations between adherence to antihypertensive drug therapy and factors such as patients' age, gender, comorbidity and type of antihypertensive drug class [8, 9], however, the joint impact of these factors have not been evaluated together in a single cohort.

Most studies assessed adherence to antihypertensive drug classes in patients with newly-diagnosed hypertension [13]. Patients with pre-existing hypertension are expected to have different medication-taking behaviours compared with newly-diagnosed patients [13]. The impact of switching from one antihypertensive drug class to another on a patient's adherence to overall antihypertensive drug therapy (therapy adherence) as well as to a particular antihypertensive drugs class (class adherence) has not been widely studied [8, 9]. Assessing adherence to individual antihypertensive drug classes without considering adherence to overall antihypertensive drug therapy limits the applicability of research findings from most previous studies as the majority of hypertensive patients are prescribed more than one antihypertensive drug class for their BP control [2]. Many studies have transformed adherence into a binary variable, using a cut-off point of 80%. Furthermore, a simple binary measure for adherence [8, 14] assumes patients over a wide range of adherence values (PDC 0-80%) to have same medication-taking behaviour, and thus may potentially misclassify/misjudge a patient's adherence behaviour.

These factors limit the application and generalisability of previous study results to patient medicine-taking behaviour in real practice. To add to what is known about adherence in hypertension, this study assessed the association between patient characteristics and adherence to both overall antihypertensive therapy and individual drug classes by applying a robust analytical method to analyse adherence as a continuous variable in patients with both newly diagnosed and pre-existing primary hypertension as an approach to produce more accurate and generalisable findings.

Methods

Study design and data source

This retrospective cohort study used data from the UK Clinical Practice Research Datalink (CPRD) database [15] from April 2006 to March 2013, as it was the most updated date for the availability of CPRD data at the time of the study. CPRD is a primary care database

containing longitudinal electronic clinical data of more than 13.7 million patients including information about patients' demographics, medical conditions, diagnoses, prescribed medications, vaccination and laboratory tests. By March 2015, CPRD included 5.4 million active patients from 685 primary care practices across the UK [16]; it covers about 8.5% of the UK population and is considered to be broadly representative in terms of patient and practice characteristics [17]. This study protocol was approved by the Independent Scientific Advisory Committee of CPRD database (protocol number 13_150).

Study cohort

Adults (≥18 years old) with a diagnosis of primary hypertension and at least two antihypertensive drug prescriptions after the diagnosis date during the study period were included in this study. Included patient needed to have at least one year of CPRD records before and after the date of their first-ever antihypertensive drug prescription (index date) during the study period. Sporadic users who were prescribed only one antihypertensive prescription were excluded [13]. In order to ensure that treating hypertension is at least one of the potential indications of the prescribed antihypertensive drugs, participants were required to have their antihypertensive drugs prescribed on or after their hypertension diagnosis date.

Patients with history of cardiovascular diseases (CVDs) prior to the index date were excluded because the presence of CVDs may affect the choice of antihypertensive drugs (indication bias) and patients' medication-taking behaviours (i.e., higher adherence as they are more willing to follow medical instructions) [18, 19]. Patients who were initiated on multiple antihypertensive drugs (either as fixed-dose combination or multiple pills) on the index date were also excluded as it was not possible to assign patients into a particular antihypertensive drug class which in turn conflicted with the study's objective of measuring a patient's adherence to any antihypertensive drug therapy. Indeed, these patients have often been excluded from previous adherence studies as they were reported to be at high risk of

HT-related complications, having higher BP value and hence would have different medication-taking behaviours [2, 20, 21].

Measurement of adherence

Individuals in the cohort were followed from the index date to the earliest of: study end date, patient transferred out of the dataset (e.g. left the practice), or patient's death; during this period, all antihypertensive prescriptions issued were retrieved and the duration of each prescription was calculated. Antihypertensive drugs were further divided into six classes: angiotensin-converting enzyme inhibitors (ACEIs), calcium-channel blockers (CCBs), diuretics, angiotensin receptor blockers (ARBs), beta-blockers (BBs), and "Others" (including vasodilators, centrally acting drugs, alpha-blockers).

A commonly used adherence measure [22], *Proportion of Days Covered* (PDC), was used as a 'proxy' for adherence in this study, and both antihypertensive 'therapy adherence' and 'class adherence' were measured. Individual patients' adherence to any antihypertensive drug therapy (PDC for therapy adherence) during the study period was calculated by dividing the '*total number of days covered with any antihypertensive drug'* by the '*number of days in the follow-up period'* [22]. Likewise, adherence to a specific antihypertensive drug class (PDC for class adherence) in each prescribing episode of a class was calculated by dividing the '*total number of days covered with an antihypertensive class*' by the '*number of days in a prescribing episode of that class*'.

The prescribing episode for a class was the duration when a patient was consecutively prescribed with the same antihypertensive drug class, starting from the date of a patient's first-ever prescription of the class during study period to the final date covered by the antihypertensive class. Multiple episodes can be identified in one patient's follow-up period, as patients may discontinue or switch to other drug classes.

Study covariates

Baseline characteristics of patients, including patients' demographics (age, gender, and socioeconomic status), disease status (comorbidity, hypertension status) and their drug use status (type of antihypertensive drug class, antihypertensive drug use status [pre-existing or new users]) on the index date were included as covariates that may be associated with patients' adherence. Furthermore, whether patients have been switched from their antihypertensive drug class was also included as a study covariate. To account for the variations in patients' follow up time, which resulted from differences in patients' study entry and exit dates, individual patient's follow up time was included as a covariate in the regression model both as a continuous and as a categorical variable.

Townsend deprivation score [23] ranging from one to five (one being least deprived and five most deprived) was used a proxy for individual patients' socioeconomic status (SES). Individual's comorbidity status was measured by the Charlson comorbidity index (CCI) [24]. Hypertension status, i.e. pre-existing (prevalent) or newly-diagnosed (incident) hypertension was judged by whether a patient had any hypertension-related diagnosis codes in the year prior to the first hypertension diagnosis code identified during the study period [25].

Similarly, antihypertensive drug use status, i.e. pre-existing (prevalent) or new (incident) users of a specific antihypertensive class was judged by whether any antihypertensive class was issued in the year prior to the index prescription date identified during the episode. Switching was defined as stopping the initial antihypertensive class and starting another class.

Data analysis

Descriptive statistics were used to describe patient-related factors at baseline. Mean with standard deviation (SD) and median with interquartile range (IQR) were used to present normally and non-normally distributed continuous variables, respectively; proportion was

used to present categorical variables. The association between individual patient characteristics and the non-normally distributed PDC was first tested in non-parametric univariate analyses, including Spearman's rank correlation test for continuous variables (age, follow-up time), Wilcoxon rank sum (Mann-Whitney) and Kruskal-Wallis tests for binary and categorical variables.

The influence of all study covariates on therapy and class adherence was assessed by using two generalised linear models (GLM) with gamma family and log link function, with the dependent variable as 'PDC for antihypertensive drug therapy' and 'PDC for each episode of antihypertensive classes', respectively. The results were presented as regression coefficients and 95% confidence interval (95%CI). The models' goodness of fit, in terms of the appropriateness of the chosen family and link function, was checked using the modified Park test [26] and Pregibon Link test [27].

Results

Baseline characteristics

Overall, 176,835 adults with primary hypertension were included in this study with 371,605 prescribing episodes of the six antihypertensive classes identified during the follow-up period. The mean age of patients at baseline was 60.8±13.6 years, 55.6% (n=98,320) were female, 53.4% (n=94,430) were newly diagnosed hypertensive patients and 51.0% (n=90,186) were new users of antihypertensive drugs. The median follow-up duration was 5.3 (IQR: 3.1, 6.5) years. Of the 371,605 prescribing episodes, the most commonly prescribed class episodes were ACEIs (29.7%) and CCBs (25.1%). Patients' characteristics and drug use status were significantly different across the episodes of six antihypertensive classes (Table 1).

Proportion of days covered

Both individual patients' PDCs for antihypertensive drug therapy overall (Figure 1) and PDCs for antihypertensive class in each episode (Figure 2) were not normally distributed. Although the median PDC was 93.3% (IQR: 47.3%, 100%) and 98.3% (IQR: 86.5%, 100%) for therapy and class adherence, respectively; 20.0% of patients' therapeutic adherence and 38.4% of prescribing episodes' class adherence were suboptimal (PDC<80%). Mean therapy and class adherence was 87%±22.2 and 73%±33.8, respectively.

Univariate analyses of factors influencing adherence

The univariate analyses demonstrated that all the covariates were significantly associated with PDC for therapy adherence in the study cohort and with PDC for class adherence in each episode (Table 2). Patients who were initiating antihypertensive therapy on CCBs had the highest PDC for therapy adherence (median: 98.6%, IQR: 86.5%, 100%). On the other hand, the median PDC for class adherence in the prescribing episodes of ARBs (median: 97.4%, IQR: 74.2%, 100%) was the highest amongst all antihypertensive drug classes, followed by ACEIs (median: 95.7%, IQR: 51.3%, 100%).

Both higher therapy and class PDCs were associated with increasing age, lower deprivation, prevalent drug users, and higher comorbidity index (CCI≥2). Male gender, being pre-existing hypertensive patient were associated with higher PDCs in the episodes of antihypertensive classes but lower PDCs for patients' overall therapy adherence. Switching between antihypertensive drug classes was also associated with lower PDC for therapy adherence.

Multivariate analyses of factors influencing adherence

The results from the GLM analysis indicated that all the patient characteristics were independent factors for both patients' adherence to antihypertensive therapy and to a specific drug class in each episode (Table 3).

Being female, having pre-existing hypertension, previous utilisation of antihypertensive medicines, and older age were associated with higher PDC for patients' antihypertensive therapy; on the other hand, higher deprivation index, high comorbidity scores (CCI≥2), and switching of antihypertensive drug class were associated with lower PDC of patients' antihypertensive therapy. Patients who were initiated with ACEIs and ARB as the index drug class during the study period; their PDCs for therapy adherence significantly increased by 4% and 3% ($p<0.001$), respectively.

Similarly, pre-existing hypertension, pre-existing antihypertensive drug user, and older age were also associated with a higher PDC for class adherence in each episode; on the other hand, being female, higher deprivation index, and high comorbidity scores (CCI≥2) were associated with lower a PDC for class adherence. Comparing between different antihypertensive drug classes, the highest PDC was in the episodes started from ARBs (13%, $p<0.001$), followed by ACEIs (8%, $p<0.001$); and the PDC for class categories "Others" was the lowest (11%, $p<0.001$).

Both class and therapy PDCs significantly changed over patients' follow-up time. There was a significant declining trend in class PDC across follow-up time categories with an average decline of 1.4% for each year increase in follow up time. Whereas for therapy PDC, although there was an average increase of patients' adherence to any antihypertensive therapy by 0.7% for each year increase in follow up time, the effect across follow up time categories were different.

The fitted multivariate GLM regression models can predict both the mean therapy and class PDCs for any patient with a particular set of characteristics included in the model. For instance, the predicted mean PDC of diuretics in the episodes for a 50-year old, female patient, with a deprivation index of 2 and comorbidity score ≥2, having diuretics as the index antihypertensive drug class, being a new antihypertensive drug user, having pre-existing hypertension, and four years of follow-up time, is 67.7% (95%CI: 66.8%, 69.5%).

Discussion

Main findings

This study assessed adherence to both individual antihypertensive drug classes and overall antihypertensive therapy using longitudinal data over a seven-year period. To our knowledge, this study is the only study that has collectively analysed adherence, as a continuous variable, to both antihypertensive drug classes and overall therapy over a long period in a population of both new and existing hypertensive patient; thus providing generalisable findings by overcoming the aforementioned limitations of the previous studies. Although no similar studies were found for direct comparison of the study findings, the findings were compared with results from various studies. Overall findings are not dissimilar to these earlier studies, but now we can more confidently describe adherence behaviours in both incident and prevalent populations and better understand the relationship between individual drug class and overall therapy adherence.

The median PDC at first glance may appear generally high, but the other summary measures, despite their limitations, (such as mean and proportion with PDC<80%) demonstrated a sub-optimal PDC level that is comparable with other adherence studies [22]. The overall mean PDC for antihypertensive drug class in each prescribing episode was 73% and about 40% episodes had PDC<80%. Although these results are comparable with the mean class adherence of 67% and PDC<80% of 36% reported by a systematic review of 139 observational studies of adherence to antihypertensive drug classes [28], the follow-up time over which adherence was measured in the systematic review was only one year which provided limited insights into the dynamic nature of adherence beyond one year. However, this current study examined adherence over seven years and has provided deeper understanding of patients' behaviours in taking their antihypertensive medications. Class adherence declined steadily, unlike therapy adherence that showed a different pattern consisting of significant reduction in the early course of therapy (>2-3 years), followed by insignificant change (>3-5 years) then a significant increase afterward (>5 years).

Furthermore, a recent observational study, assessing association between patients' characteristics and adherence to overall antihypertensive drug therapy, also reported a similar high, overall median adherence to overall antihypertensive drug therapy of 96%, with more than 75% being considered adherent (PDC≥80%) [29], however, again this study was limited by short follow-up of one year as well as analysing adherence as a binary variable.

Factors associated with patients' adherence

Medications and clinically related factors

Type of antihypertensive drug class was a significant predictor for adherence to both antihypertensive drug classes and therapy; ARBs followed by ACEIs were associated with the highest-class adherence, while diuretics and BBs were associated with the lowest. This confirms the historical findings from many other adherence studies [21, 30, 31], which has been attributed largely to the more favourable tolerability profile of ARBs and ACEIs compared with other antihypertensive drug classes. However, once switching was considered in measuring adherence to overall antihypertensive drug therapy, ACEIs rather than ARBs had the highest adherence, with BBs no longer having lower adherence compared with diuretics. This implies that all the previous historical findings were indeed biased by not considering switching in measuring adherence, especially given the better tolerability of ARBs compared with others [31], and hence less switching and better adherence profile of ARBs if switching was not considered.

Lower adherence to antihypertensive drug classes and therapy was observed in newly diagnosed hypertensive patients and new antihypertensive drug users. Differences in beliefs, perceptions and attitudes towards hypertension and antihypertensive drug therapy between incident and prevalent patients could explain the observed disparity in adherence behaviour between these two groups of patients since prevalent patients may have passed the stages of lack of belief in the necessity of treating hypertension [32]. Furthermore,

patients' concerns and fears about antihypertensive drugs' adverse effects in the early stages of treatment in the case of incident patients may act as a barrier of adherence to antihypertensive drugs, particularly when patients' hold the belief that a drug's side effects outweigh any potential future benefits [33].

This study found a negative association between adherence to antihypertensive drug classes/therapy and presence of comorbidities. It has been reported that patients with no comorbidity were 29% more likely to be adherent compared with those with a high comorbidity score [34]. The negative association between high comorbidity and adherence could be partly explained by comorbidity-related polypharmacy, as additional medications are needed in response to increasing comorbid conditions [35], which has been found to decrease adherence [36]. Importantly, it appears that this has to exceed a limit before comorbidities having any negative impact of adherence, as it is evident by the fact that both class and therapy adherence were decreasing only for patients with high comorbidity score (CCI≥2).

In previous studies [7, 37], switching between antihypertensive drug classes was associated with lower adherence to any antihypertensive drug therapy. This association could be related to many switching-related concerns that would potentially decrease patients' adherence, such as changes in product packaging and tablet appearance [38] and taste [35], differences in adherence profiles of the various antihypertensive drug classes [8], and impairing patient's confidence in drug therapy [39]. Furthermore, it has been shown that patients' concerns about switching may produce a nocebo effect (i.e. patients' negative perceptions may cause negative outcomes) [40].

Demographic factors

Patients' demographics, such as age, gender and SES, were also significant predicators for antihypertensive drug adherence. Poor SES has been recognised by the WHO as one of the

potential factors for patients' non-adherence to antihypertensive drugs [41]. An American cohort study has found that increasing in patients' income quintile, as a proxy for SES, was associated with a 10% increase in the proportion of adherent patients (OR: 1.10, 95%CI: 1.08, 1.12) [34]. Furthermore, a recent retrospective cohort study, which included more than 30,000 adult patients, assessed the association between patients' characteristics and medication adherence across eight diseases, including hypertension, and found a higher adherence level in those living in higher SES (lower deprivation) [29].

Females, in general, have been consistently shown to be less adherent to antihypertensive drug classes [29, 42, 43]. Although similar finding was observed in the current study, importantly this was not the case for adherence to antihypertensive drug therapy as females had higher adherence than males. This could be explained by not allowing/considering switching in measuring adherence to antihypertensive drug classes, especially giving the higher switching rates in females [44]; i.e., once patients have been switched to another antihypertensive drug class they were considered as non-adherent to the initial drug class by definition as they have stopped taking it, but obviously patients have been adherent to the antihypertensive drug therapy overall as they continued to take the new drug class while stopped the initial class. This demonstrates how insights into patients' medication taken behaviours could be biased by purely measuring adherence to antihypertensive drug classes without considering the overall antihypertensive drug therapy, which is more influential on controlling BP.

Strengths and limitations

One of the major strengths of the current study is analysing adherence as a continue measure by applying an advanced statistical technique (GLM) unlike most of the previous studies [8, 9] which measured and analysed adherence as a binary variable using a non-empirical, arbitrary cut-off point of 80% [8, 14]. Dichotomisation of adherence simplifies statistical analysis, presentation and interpretation of results [45] but incurs several

disadvantages. Dichotomisation of a continuous variable is often associated with loss of information [46] that can lead to loss of both estimation efficiency and power in hypothesis testing [45, 47] due to a reduction in the number of degrees of freedom [48]. Furthermore, although the 80% cut-off point for optimal adherence has been generally used and linked with clinical outcomes in previous studies, the optimal adherence cut-off point may be higher than 80%, as BP has found to continuously reduce with increases in adherence from 80% to 100% [49].

Therefore, the International Society for Pharmaceutical and Outcomes Research [48] has recommended against converting continuous adherence data into binary data. On a related notes, previous studies [50, 51] that analysed adherence as a continuous measure have used inappropriate statistical methods to perform the analysis such as ordinary least square (OLS) regression. OLS is considered an inappropriate method because it requires a normally distributed outcome variable that is almost violated by the skewed distribution of the continuous adherence measure.

Another main strength of this study lies in measuring adherence to both antihypertensive drug classes and any antihypertensive drug therapy using a large population dataset of both incident and prevalent hypertensive patients over a long period. Furthermore, applying an advanced statistical technique (GLM) to analyse the association between adherence (as a continuous variable) with a wide range of patient related factors. This approach has not been observed in previous adherence studies and rendered the findings more generalisable to the wider hypertensive population. For instance, measuring adherence to both antihypertensive drug classes and any antihypertensive drug therapy has increased the applicability of the study findings to the real-world management of hypertension, given the increased proportion of hypertensive patients who are prescribed more than one antihypertensive drug classes to control their BP [2].

Furthermore, failure to allow for switching in measuring class adherence in previous studies, implies that the patient failed to take the drug as recommended [9], which, in fact, may not be the case because patient's switching is often recommended by physicians in response to treatment failure or side effects [13]. Therefore, measuring adherence to any antihypertensive drug therapy (therapy adherence), in this current study, helped to avoid misunderstanding of patients' medication-taking behaviours toward a particular antihypertensive drug class and provided more insights.

Additionally, the model generated from using GLM method in this study could potentially be applied as a predication tool for identifying patients at risks of poor adherence who could possibly then be targeted for adherence improving interventions; however, this requires further validation and evaluation research.

However, a number of limitations need to be acknowledged. Although a wide range of demographics and clinically related factors were considered in this study, bias due to unmeasured confounders, such as dosing history, cannot be ruled out due to the retrospective nature of the study design. Although some of the antihypertensive drugs could be used to treat other conditions alongside hypertension, the criterion of antihypertensive drugs' prescription date always being on or after the hypertension diagnosis date has ensured that treating hypertension was at least one of the drug's potential indications.

In addition, the CPRD contains only prescribed data, therefore adherence was measured indirectly by PDC as a proxy, which may lead to further overestimation of medication adherence. Furthermore, overestimation of adherence might have resulted also from excluding patients on multiple therapies at the index date as they might have higher risk of poor adherence.

Another limitation, which applies to any secondary database analysis, includes measuring adherence using secondary databases. This has been validated with other methods of adherence measurement such as electronic devices, patients' self-reports and pill counts [52, 53], and no substantial differences between dispensing and prescribing datasets were found [54]. Given the different methods to measure medication adherence using secondary databases, it could be argued that each method may produce different results. However, Hess *et al* (2006) [55] in their comparison of the various methods of measuring adherence using secondary databases found that all the methods provide comparable values.

Among the adherence measures, medication possession ratio (MPR) and PDC were the best predictors of patients' hospitalisations [56]. PDC is considered preferable than MPR as it provides more conservative estimates of adherence, especially in the presence of therapeutic switching or concurrent drug therapy [57, 58], even though adherence alone does not provide information on whether patients benefit from the increased use of medicines.

Conclusions

Overall, adherence to antihypertensive medications was suboptimal among patients with primary hypertension. A set of patient-level factors has been identified as potential determinants for patients' adherence to antihypertensive drugs that would potentially assist to identify patients at risk of poor adherence. Subsequently, those patients can be targeted for adherence improving interventions and/or more intensive follow-up by healthcare professionals to improve their adherence level.

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Tables

Table 1. Patient characteristics at first-ever antihypertensive drug class episodes

Covariates	ACEIs	CCBs	Diuretics	BBs	ARBs	"Others"	Total
Number of episodes (%)	110,493 (29.7)	93,119 (25.1)	71,883 (19.3)	42,164 (11.4)	39,862 (10.7)	14,084 (3.8)	371,605
Mean age (±SD) years	57.9±12.4	64.8±12.0	67.4±12.1	61.5±13.1	62.2±12.6	64.7±14.1	62.2±12.9
Gender (%)[a]							
Male	61,655 (55.8)	46,839 (50.3)	23,865 (33.2)	17,709 (42.0)	18,695 (46.9)	6,648 (47.2)	177,627 (47.8)
Female	48,838 (44.2)	46,280 (49.7)	48,018 (66.8)	24,455 (58.0)	21,167 (53.1)	7,436 (52.8)	193,978 (52.2)
Townsend deprivation score (quintile) (%)[b]							
1 (Least deprived)	28,176 (25.5)	22,535 (24.2)	17,252 (24.0)	11,131 (26.4)	11,042 (24.5)	3,451 (24.5)	97,361 (26.2)
2	26,739 (24.2)	22,162 (23.8)	17,539 (24.4)	10,372 (24.6)	10,045 (25.2)	3,324 (23.6)	86,212 (23.2)
3	22,983 (20.8)	18,996 (20.4)	15,455 (21.5)	8,728 (20.7)	81,72 (20.5)	3,042 (21.6)	73,578 (19.8)
4	19,889 (18.0)	17,227 (18.5)	13,298 (18.5)	7,547 (17.9)	6,418 (16.1)	2,577 (18.3)	63,544 (17.1)
5 (Most deprived)	12,707 (11.5)	12,292 (13.2)	8,338 (11.6)	4,385 (10.4)	4,186 (10.5)	1,648 (11.7)	50,910 (13.7)
Median follow up time (IQR, years)[b]	4.6 (2.9, 6.4)	4.4 (2.6, 6.4)	5.6 (3.6, 6.9)	6.8 (4.6, 7.0)	6.5 (4.4,6.9)	6.5 (4.2, 6.9)	5.1 (3.2, 6.8)
CCI (%)[a]							
0	65,412 (59.2)	58,292 (62.6)	44,208 (61.5)	30,400 (72.1)	22,522 (56.5)	7,535 (53.5)	229,280 (61.7)
1	24,529 (22.0)	18,251 (19.6)	14,520 (20.2)	6,072 (14.4)	9,288 (23.3)	3,451 (24.5)	75,807 (20.4)
≥2	20,552 (18.6)	16,575 (17.8)	13,155 (18.3)	5,692 (13.5)	8,052 (20.2)	3,098 (22.0)	66,517 (17.9)
Hypertension status (%)[a]							
Incident cases	62,650 (56.7)	51,960 (55.8)	26,165 (36.4)	7,252 (17.2)	6,458 (16.2)	2,225 (15.8)	165,364 (44.5)
Prevalent cases	47,843 (43.3)	41,159 (44.2)	45,718 (63.6)	34,912 (82.8)	33,404 (83.8)	11,859 (84.2)	206,241 (55.5)
Drug use status (%)[a]							
Incident users	72,925 (66.0)	60,993 (65.5)	29,184 (40.6)	9,698 (21.0)	9,328 (23.4)	3,606 (25.6)	193,978 (52.2)
Prevalent users	37,568 (34.0)	32,126 (34.5)	42,699 (59.4)	33,310 (79.0)	30,534 (76.6)	10,478 (74.4)	177,627 (47.8)

(Note) [a] p<0.001 from McNemar test; [b] p<0.001 Kruskal-Wallis test; **IQR**: interquartile range; **CCI**: Charlson comorbidity index; **ACEIs**: angiotensin converting enzyme inhibitors; **ARBs**: angiotensin receptor blockers; **CCBs**: calcium channel blockers; **BBs**: beta-blockers

Table 2. Univariate analysis of the patient related factors with class and therapy PDC

Covariates	Class PDC		Therapy PDC		Statistical test
	Median (IQR)	p-value	Median (IQR)	p-value	
Index drug class					
ACEIs	95.7 (51.3, 100)		98.3 (85.8, 100)		
CCBs	94.3 (50.4, 100)		98.6 (86.5, 100)		
Diuretics	90.6 (44.2, 100)	P=0.001	97.8 (85.9, 100)	P=0.0001	Kruskal-Wallis test
BBs	86.7 (24.3, 100)		98.5 (88.0, 100)		
ARBs	97.4 (74.2, 100)		98.3 (88.7, 100)		
"Others"	84.4 (26.7, 100)		98.5 (86.8, 100)		
Gender					
Male	94.2 (51.1,100)	P<0.001	97.9 (85.7, 100)	P<0.001	Wilcoxon rank sum (Mann-Whitney) test
Female	93.6 (43.7, 100)		98.7 (87.2, 100)		
Townsend deprivation score (quintile)					
1 (Least deprived)	95.3 (48.3, 100)		98.8 (89.4, 100)		
2	94.6 (47.8, 100)		98.6 (88.2)		Kruskal-Wallis test
3	94.2 (47.7, 100)	P=0.001	98.3 (86.8, 100)	P=0.0001	
4	93.0 (46.9, 100)		97.9 (84.1, 100)		
5 (Most deprived)	89.6 (45.1, 100)		96.6 (78.1, 100)		
Drug use status					
Incident users	92.7 (37.9, 100)	P<0.001	98.2 (82.7, 100)	P<0.001	Wilcoxon rank sum (Mann-Whitney) test
Prevalent users	94.9 (57.0, 100)		98.4 (89.4, 100)		
Hypertension status					
Incident cases	93.3 (39.3, 100)	P<0.001	98.5 (84.0, 100)	P= 0.0079	Wilcoxon rank sum (Mann-Whitney) test
Prevalent cases	94.3 (53.1, 100)		98.2 (88.0, 100)		
Switching index drug					
No	NA	NA	98.7 (88.9, 100)	P<0.001	Wilcoxon rank sum (Mann-Whitney) test
Yes			96.7 (78.4, 100)		
CCI					
0	93.7 (45.5, 100)		98.1 (85.8, 100)		Kruskal-Wallis test
1	94.3 (50.6, 100)	P=0.001	98.5 (87.1, 100)	P=0.0001	
≥2	94.3 (49.1, 100)		98.9 (87.7, 100)		
Age (years)	0.08*	P<0.001	0.15*	P<0.001	Spearman's rank correlation test
Follow up time (years)	0.03*	P<0.001	0.02*	P<0.001	Spearman's rank correlation test

(Note) PDC: proportion days covered; **IQR**: interquartile range **;** **ACEIs**: angiotensin converting enzyme inhibitors; **ARBs**: angiotensin receptor blockers; **CCBs**: calcium channel blockers; **BBs**: beta-blockers; **CCI**: Charlson comorbidity index; **NA**: not applicable

Table 3. Results from the GLM regression of the patient related factors with class and therapy adherence

Covariates	Class PDC		Therapy PDC	
	Coefficients (95%CI)	p-value	Coefficients (95%CI)	p-value
Index drug class				
Diuretics	1.0		1.0	
ACEIs	0.08 (0.074, 0.087)	<0.001	0.04 (0.035, 0.043)	<0.001
CCBs	0.052 (0.04, 0.06)	<0.001	0.02 (0.017, 0.025)	<0.001
BBs	-0.09 (-0.10, 0.-0.084)	<0.001	0.016 (0.011, 0.020)	<0.001
ARBs	0.13 (0.12, 0.14)	<0.001	0.03 (0.023, 0.032)	<0.001
"Others"	-0.11(-0.13, -0.09)	<0.001	-0.008 (-0.011, 0.0096)	0.869
Gender				
Male	1.0		1.0	
Female	-0.034 (-0.38, -0.029)	<0.001	0.004 (0.0012, 0.0060)	<0.001
Townsend deprivation score (quintile)				
1 (Least deprived)	1.0		1.0	
2	-0.003 (-0.009, 0.002)	0.294	-0.009 (-0.012, -0.01)	<0.001
3	-0.002 (-0.009, 0.004)	0.452	-0.013 (-0.02, 0.01)	<0.001
4	-0.008 (-0.012, -0.001)	0.022	-0.025 (-0.03, -0.02)	<0.001
5 (Most deprived)	-0.02 (-0.03, -0.01)	<0.001	-0.05 (-0.06, -0.04	<0.001
Drug use status				
Incident users	1.0		1.0	
Prevalent users	0.13 (0.12, 0.14)	<0.001	0.06 (0.055, 0.065)	<0.001
Hypertension status				
Incident cases	1.0		1.0	
Prevalent cases	0.02 (0.008, 0.025)	0.02	0.03 (0.028, 0.04)	<0.001
CCI				
0	1.0		1.0	
1	0.0006 (-0.0049, 0.006)	0.837	0.03 (-0.00002, 0.0059)	0.052
≥2	-0.02 (-0.021, -0.0092)	<0.001	-0.046 (-0.078, - 0.0020)	0.004
Age (years)	0.003 (0.0028, 0.0033)	<0.001	0.0032 (0.0032, 0.0033)	<0.001
Follow up time (years)	-0.014 (-0.016, -0.013)	<0.001	0.007 (0.006, 0.0073)	<0.001
Follow up time categories (years)				
≤2	1.0		1.0	
>2-3	-0.017 (-0.022, -0.012)	<0.001	-0.08 (-0.14, -0.03)	0.001
>3-4	-0.024 (-0.030, -0.019)	<0.001	-0.04 (-0.09, 0.01)	0.148
>4-5	-0.035 (-0.040, -0.030)	<0.001	-0.02 (-0.07, 0.03)	0.756
>5	-0.035 (-0.039, -0.030)	<0.001	0.18 (0.21, 0.14)	<0.001
Switching index drug				
No	NA	NA	1.0	
Yes			-0.043 (-0.046, -0.040)	<0.001

(Note) PDC: proportion days covered; **ACEIs**: angiotensin converting enzyme inhibitors; **ARBs**: angiotensin receptor blockers; **CCBs**: calcium channel blockers; **BBs**: beta-blockers; **CCI**: Charlson comorbidity index; **NA**: not applicable

Figures

Figure 1 Cumulative proportion of patients' adherence to any antihypertensive drug therapy

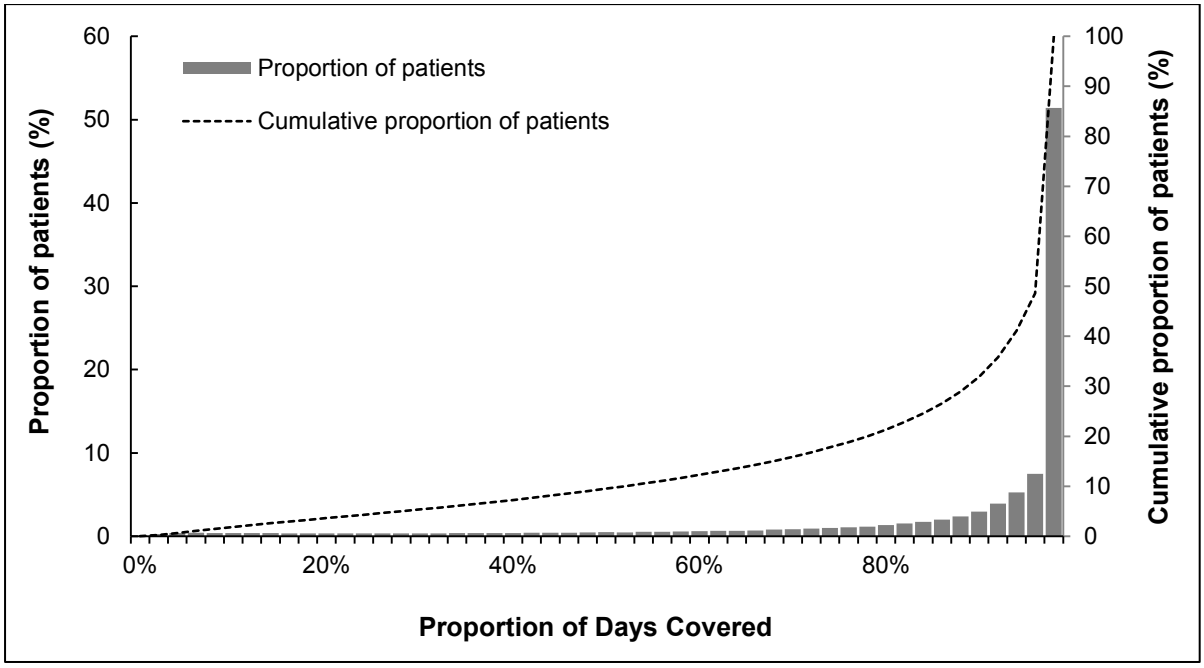

Figure 2 Cumulative proportion of adherence of the episodes of the six antihypertensive drug classes