Patient Preference and Adherence

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ORIGINAL RESEARCH

Analysis of Adherence to Antihypertensive Drugs in Chinese Patients with Hypertension: A Retrospective Analysis Using the China Health Insurance Association Database

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Objective: To analyze the adherence to antihypertensive drugs in Chinese patients with hypertension and the factors associated with the drug adherence.

Methods: The data for this analysis were obtained from the 2014 China Health Insurance Association (CHIRA) database. The study included 64,576 patients aged ≥18 years who were prescribed one of the seven antihypertensive drugs included in the study in their first prescription in 2014 and were observed for ≥180 days. The medicine possession ratio (MPR) was calculated and taken as the measure of treatment adherence. MPR values <0.3, 0.3 to <0.5, 0.5 to <0.8, and ≥0.8 were considered treatment adherence very low, low, intermediate, and high, respectively. Descriptive statistics were used to present baseline data and treatment adherence rate. Multiple regression models were used to determine independent factors which can affect the treatment adherence rate. *P*-value <0.05 was considered significant.

Results: Among the study antihypertensive drugs, amlodipine (33.98%), metoprolol (25.04%), and nifedipine (17.15%) were the frequently prescribed drugs. Nifedipine controlled release tablet had the highest MPR (0.61), followed by valsartan (0.53), valsartan/amlodipine fixed-dose combination (0.50), indapamide (0.40), and amlodipine (0.39), whereas benazepril (0.27) and metoprolol (0.19) had the lowest MPR. Higher reimbursement ratio, regular tertiary hospitals visits, lower age, and lower daily medical cost positively affected treatment adherence, whereas longer duration of illness and higher daily average cost affected treatment adherence negatively.

Conclusion: Our study assessed that prescribing more cost-effective, long-acting antihypertensive drugs, and raising the reimbursement ratio were associated with a better treatment adherence in Chinese patients with hypertension.

Keywords: treatment adherence, medicine possession ratio, hypertension, antihypertensive treatment

Introduction

Hypertension (HTN) is the most prevalent and preventable risk factor for cardiovascular diseases (CVDs) and CVD-related mortality.[1] It majorly accounts for global all-cause mortality; 10.5 million deaths in 2016 were related to elevated systolic blood pressure.[2,3] The global burden of hypertension data (1990–2015) of population with systolic blood pressure 110–115 mmHg revealed that globally, approximately one in every four adults is suffering from HTN.[1] In addition, a survey conducted between

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2012 and 2015 showed that in China, 23.2% of total population aged >18 years had HTN, whereas 41.3% had preHTN.[4] Clinical studies have shown that efficient HTN control (<140/90 mmHg) reduces CVD- and stroke-associated morbidity and mortality.[5,6]

Although several classes of antihypertensive (AHT) drugs are available and prescribed as per the guidelines to control HTN,[7–10] their effectiveness is detrimentally affected by poor treatment adherence, which results in increased mortality, cardiovascular morbidity, rate and length of hospitalization, overall medical expenditure, and exacerbated quality of life.[11–14] The World Health Organization defines adherence as

> the extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a health-care provider.[15]

Nonadherence to AHT medication has become a global cause of concern as it adversely affects the efforts made by health-care professionals and policy makers to control HTN.[16]

Previously, treatment adherence was investigated using pill counts, clinical reports, prescriptions, and patient-reported information.[17] However, in recent years, new preferred approaches to measure treatment adherence have been developed, including patient-reported questionnaires, scales, medicine possession ratio (MPR), and proportion of days covered.[17] MPR, defined as the percentage/proportion of days' supply obtained until the last refill (refill interval) or a specific time period (fixed refill),[18,19] is an established measure of AHT treatment adherence.[20–22] It is generally <1; however, may exceed 1.0 if the patients obtain refills prior to their supply running out.[23] Despite a few limitations (eg, nonavailability of clinical data, etc), pharmacy databases managed by a health-care organization, private as well as government insurance companies serve as a good source of data for evaluating treatment adherence, as they provide "real-world" evidence and the data can be easily retrieved for analysis.[18,24]

Several studies have analyzed adherence to AHT drugs in different regions of the world.[11,16,25–28] However, there is scarcity of evidence on AHT treatment adherence among the Chinese population in real-world settings.[25,29] Ethnic diversity is reported to affect pharmacological actions of AHT drugs,[30] and regional/cultural differences in health care may influence AHT drug-taking behavior of patients with HTN.[31] This limits the application of treatment adherence information of one geographical region to another in true sense. Therefore, we evaluated AHT treatment adherence, in terms of MPR, and the factors affecting MPR of the seven most commonly used AHT drugs among the Chinese population in real-life settings using information extracted from the China Health Insurance Association (CHIRA) database.

Methods

Study Design

This was a retrospective analysis of data of patients with HTN taken from the CHIRA database for 2014. The CHIRA database had data of 6,560,000 patients from 77 cities, of which, data of 3,344,000 patients were excluded due to lower/missing outpatient diagnosis rate and/or higher diagnosis missing rate (Figure 1). Employee medical insurance data of 33 cities with relatively high quality (including outpatient and inpatient data) were used for the analysis.

Patients with clinically diagnosed HTN and aged ≥18 years were included in the analysis if their first prescription for 2014 had any of the following AHT drugs: benazepril, an angiotensin-converting enzyme (ACE) inhibitor; valsartan, an angiotensin receptor blocker (ARB); metoprolol, a β-blocker; nifedipine and nifedipine gastrointestinal tablets (GITs), a calcium channel blocker (CCB); amlodipine, a CCB; indapamide, a diuretic; or valsartan/amlodipine fixed-dose combination (FDC). Patients covered by employee medical insurance and patients with hypertension caused by secondary diagnosis were also included in the study. Of these patients, only those who were prescribed AHT drugs at least or more than twice were observed for ≥180 days (first prescription-last prescription) were included in the analysis. Patients with cancer, organ failure, and gestational/postoperative HTN were excluded from the analysis. The successive prescriptions were used to analyze treatment adherence. During the data extraction step, data on member eligibility (demographics); inpatient medical information—admission date/discharge date; place of service including hospital tier (tier 1, primary care hospitals; tier 2, city-level hospitals; tier 3, teaching hospitals); type, and department; length of stay; primary diagnosis according to International Classification of Disease (ICD)-10/Chinese texts; and diagnosis description); and outpatient medical information—date; place of service including hospital tier; type, and department; and primary diagnosis (ICD-10/Chinese text); services claims (drug name, drug code; prescription, examination, treatment, operation, bed, medical materials, etc; drug unit price; drug formulations; and dispensed quantity of drug), cost of each event, and other relevant information was extracted. The data for cities with outpatient diagnosis

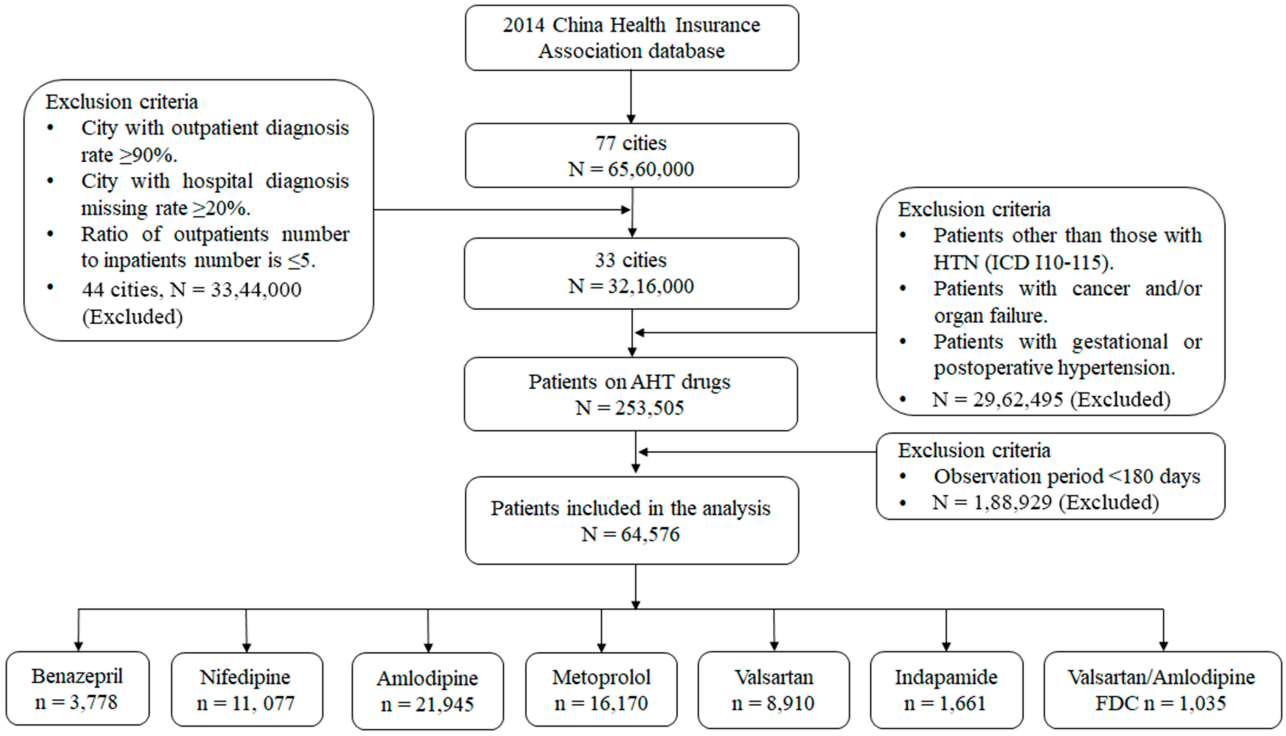

Figure 1 Study flow diagram.

missing rate of ≥90%, hospital diagnosis missing rate of ≥20%, and the ratio of outpatients number to inpatients number is ≥5. After excluding patients other than those with ICD 10 I10–115 HTN, patients with organ failure and/or cancer and/or gestational/postoperative HTN, 64,576 patients (mean age: 63.4 years; males: 51.73%; females: 48.27%) were included in the analysis.

The study was conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practice,[32] Good Practice of Secondary Data Analysis,[33] the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance Guideline on Methodological Standards in Pharmacoepidemiology,[34] and Good Epidemiological Practice.[35]

End Points

Measuring treatment adherence among study populations in terms of MPR was the primary end point of the study. The secondary end points were hospital visits and determination of the factors affecting treatment adherence.

For 2014, MPR was calculated as total days' supply of drug dispensed (excluding the last prescription) during the year divided by total days from the first prescription until the last prescription given during the observation period. Total drug supply for each study drug was calculated as the total amount of drug prescribed in 2014 divided by defined daily dose. Observation period was taken as the period between the first claim records with HTN and the last claim records due to any reason in 2014.

MPR of the seven AHT drugs was calculated for three different time periods: (1) the first study drug prescription to the last study drug prescription (drug in the first and last prescription need not be same), that is, the first goal (FG) to the last goal (LG); (2) the first study drug prescription to the last other AHT drug (an AHT drug that is not included in this study) prescription, that is, FG to the last random (LR); and (3) the first other AHT drug prescription to the last other AHT drug prescription, that is, the first random (FR) to LR. Treatment adherence was considered very low, low, intermediate, and high corresponding to MPR values <0.3, 0.3 to <0.5, 0.5 to <0.8, and ≥0.8, respectively.[12,36]

Statistical Analysis

All the analyses were performed using statistical analysis software (SAS) 9.3 version. Descriptive analysis was used for continuous variables: mean, SD, standard error (SE) and categorical variables: frequency tables: absolute and relative frequencies. MPR for FG-LR was categorized in ranges of 0≤MPR<0.3, 0.3≤MPR<0.5, 0.5≤MPR<0.8, and 0.8≤MPR<1. MPR was analyzed using descriptive statistics,

whereas factors affecting MPR were analyzed using multivariate regression analysis. Analysis of covariance was used to evaluate variation in MPR values among AHT drugs. *P*-value of <0.05 was considered significant.

Results

Study Population

Out of 64,576 patients included in the analysis, the proportion of patients in >40, 40–59, 60–79, and ≥80-year age group was 3.3%, 35.14%, 50.65%, and 10.98%, respectively. Eastern, midland, and western regions contributed 89.46%, 3.95%, and 6.59% of the study population. Of the included patients, 46.19% were from municipalities and 36.80% were from provincial capitals. The average observation duration was 290 days for all the study drugs.

Table 1 presents baseline characteristics and demographics data of patients with HTN for individual AHT drug included. The highest number of patients were receiving amlodipine (33.98%), whereas the least number of patients were taking valsartan/amlodipine FDC (1.60%). Patients receiving metoprolol were the oldest among all groups (mean age, 64.85 years). Comorbidities were present in 63.01% of the patients included in the analysis with highest proportion observed in patients receiving nifedipine GITs (76.14%) and lowest among those receiving amlodipine (53.09%).

MPR of AHT Drugs

Among all the analysis groups, nifedipine GITs treatment was associated with the highest mean MPR (0.61), whereas metoprolol had the lowest (0.19). MPR values of the study AHT drugs are given in Figure 2A. The difference observed in the mean MPR values for different AHT drugs was significant (*P*<0.0001). MPR of AHT drugs based on gender, age, city level, hospital tiers, comorbidities, and hospitalization status are presented in the Supplementary Table.

The proportions of patients with ≥0.5 MPR were shown in Figure 2B. Nifedipine GITs-treated patients had the highest proportion of MPR ≥0.5 (60.44%); whereas metoprolol-treated patients had the least proportion (11.31%). Metoprolol group had highest proportion of patients with very low treatment adherence, ie, MPR <0.3 (78.21%), whereas nifedipine had highest proportion of patients with high treatment adherence, ie, MPR ≥0.8 (40.85%), as depicted in Figure 2C.

Use of AHT Drugs

The proportion of patients receiving combination of AHT drugs was 56.27%. Among the patients included in the study, 60.86% had replacement of study drug during the observation period. The data of AHT drug usage among the study population and the associated daily cost are

Table 1 Baseline and Comorbidity Characteristics of Different Antihypertensive Drugs

	Benazepril	Nifedipine GITs	Amlodipine	Metoprolol	Valsartan	Indapamide	Valsartan/ Amlodipine
No. of patients (N)	3778	11,077	21,945	16,170	8910	1661	1035
Primary diagnosis with HTN (% of n)							
Patients with primary HTN	96.48	97.73	97.02	96.56	97.03	96.63	95.46
Patients with secondary HTN	1.11	0.48	2.09	2.12	1.54	1.51	3.48
Secondary diagnosis with HTN (% of N)	2.41	1.79	0.89	1.32	1.43	1.86	1.06
Mean observation duration (days)	291.56	295.45	290.55	293.65	291.38	293.65	289.25
Men (% of N)	55.11	50.75	49.45	50.96	50.62	52.68	52.56
Women (% of N)	44.89	49.25	50.55	49.04	49.38	47.32	47.44
Mean age (years)	63.12	63.08	63.80	64.85	62.44	64.21	62.29
*Comorbidities (% of N)	66.91	76.14	53.09	64.85	63.45	56.35	60.29
Coronary heart disease	48.91	60.96	35.77	52.58	45.44	40.28	39.23
Diabetes mellitus	39.89	43.83	27.86	28.67	35.16	31.13	32.75
Stroke	13.76	17.58	10.76	11.68	11.95	12.52	11.79
Chronic renal diseases	3.26	3.85	2.24	2.54	3.31	1.69	4.35
Peripheral vascular disease	0.82	1.27	0.52	0.72	0.79	0.66	0.97

Note: *Some patients have more than one comorbidity.
Abbreviations: HTN, hypertension; GITs, gastrointestinal tablets.

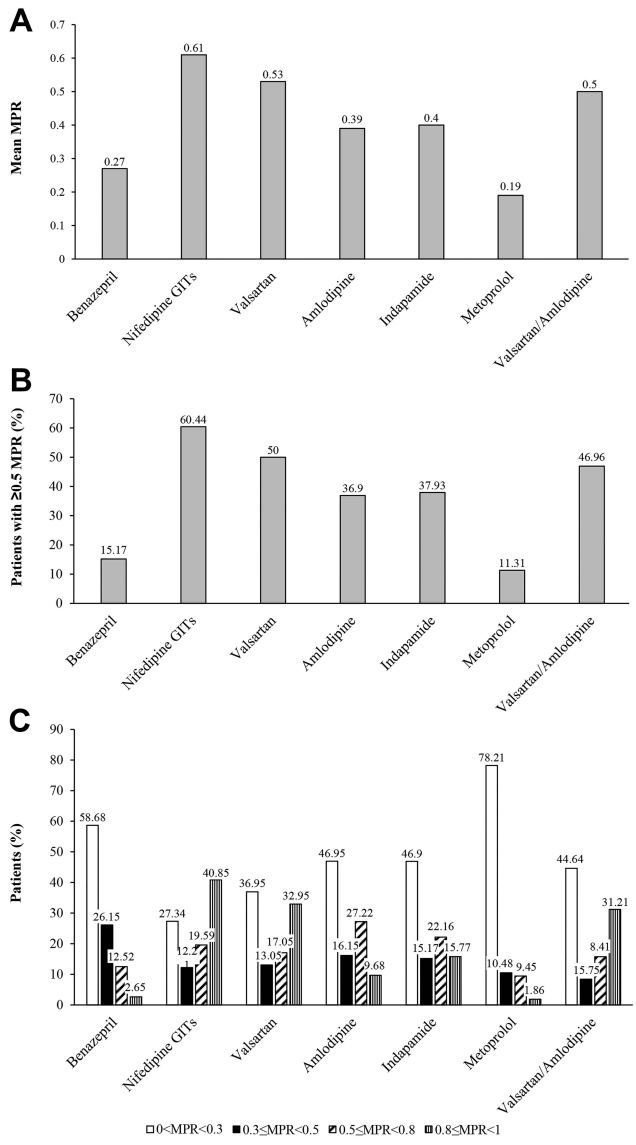

Figure 2 MPR of different AHT drugs. (**A**) Mean MPR values; (**B**) percentage of population with MPR of ≥0.5; (**C**) population distribution among different range of MPR of AHT drugs. The difference among groups was statistically significant for mean MPR and proportion of patients with ≥0.5 MPR (P<0.0001 for both). **Abbreviations:** MPR, medicine possession ratio; GITs, gastrointestinal tablets.

provided in Table 2. Proportion of patients switching to an AHT drug other than those included in this study was least in valsartan/amlodipine FDC group (30.14%) and highest in metoprolol group (46.00%), (Table 2). Among AHT drugs, indapamide had the least daily cost (0.93 yuan), whereas valsartan/amlodipine FDC had the highest daily cost (8.7 yuan).

Outpatient Visit

The number of annual per capita outpatient visit was highest for Nifedipine GITs (32.6) and lowest for valsartan/amlodipine FDC (19.73). Approximately 45.02% of patients with HTN visited the tier 1 hospitals and grassroot community units followed by tier 3 hospitals (35.82%), tier 2 hospitals (16.58%), and pharmacies (2.44%), with 0.14% of patients visiting unknown medical institutions. Table 3 presents hospital visit data of patients as per the prescribed AHT drug.

Potential Factors Affecting MPR of AHT Drugs

Factors that could have modulated MPR were evaluated using stepwise regression based on a multivariate linear regression model. The results showed that MPR was positively affected (P<0.0001 for all comparisons) by following variables: (1) age, (2) city level, (3) comorbidities (diabetes, stroke), (4) prescription of multidrug combination, (5) tier 3 hospital visits, (6) reimbursement ratio, (7) study drugs, except metoprolol, in the first prescription (Table 4). Presence of coronary artery disease (SE, 0.003; P=0.0016), times of hospitalization (SE, 0.0030; P<0.0001), and metoprolol prescription (SE, 0.0068; P<0.0001) negatively affected MPR (Table 4).

Discussion

Research on AHT treatment adherence helps understanding the current scenario of treatment adherence, designing interventions, and formulating relevant policies to improve the health outcomes of patients. To the best of our knowledge, this is the first large-scale study to determine treatment adherence for different AHT drugs in China using the CHIRA database. Given the fact that treatment adherence is influenced by demographic, region-specific, organizational, comorbidities, and medication-related variables, we also investigated the association of these factors with the recorded MPR for all AHT drugs included in the study. Our results showed poor overall AHT treatment adherence among Chinese patients with HTN and revealed that they have the highest treatment adherence for nifedipine GITs and the lowest for metoprolol. A positive association of MPR with age, city level, comorbidities, frequency of outpatient visits, and hospitalization was observed.

We used the MPR to evaluate treatment adherence among the study population, which is a globally accepted metric to retrospectively assess treatment adherence.[18,37] Other measures of treatment adherence include medication-total, adherence ratio, proportion of days covered, refill adherence, compliance rate, compliance ratio, continuous measure of medication acquisition, continuous measure of medication

Table 2 The Use of the Seven Antihypertensive Drugs Among the Patients

Variables	Benazepril N=3778	Nifedipine GITs N=11,077	Amlodipine N=21,945	Metoprolol N=16,170	Valsartan N=8910	Indapamide N=1661	Valsartan/ amlodipine N=1035
Proportion of multidrug combination in the first prescription (%)	61.83	46.06	51.52	68.92	57.12	68.27	40.19
Proportion of drug replacement (%)	62.07	61.94	51.29	63.52	61.28	77.54	48.41
Switching to benazepril (%)	–	3.77	2.21	2.03	1.76	1.93	0.77
Switching to nifedipine controlled release tablets (%)	9.95	–	3.80	6.64	9.58	6.26	2.51
Switching to amlodipine (%)	11.91	7.39	–	11.21	12.29	10.05	10.63
Switching to metoprolol (%)	9.56	8.87	8.28	–	8.73	9.39	9.47
Switching to valsartan (%)	5.11	8.01	5.12	5.05	–	5.54	8.70
Switching to indapamide (%)	1.48	1.27	0.87	1.06	0–.94	–	1.06
Switching to valsartan/amlodipine (%)	0.00	0.50	0.76	0.76	1.04	0.84	–
Switching to antihypertensive drug(s) other than the seven target drugs (%)	37.53	42.13	38.61	46.00	38.87	43.53	30.14
Daily cost of antihypertensive drugs (yuan) (%)	7.81	4.49	4.38	4.00	4.40	0.93	8.70

Abbreviation: GITs, gastrointestinal tablets.

Table 3 Hospital Visits by Patients Receiving Studied AHT Drugs

	Benazepril	Nifedipine GITs	Amlodipine	Metoprolol	Valsartan	Indapamide	Valsartan/ amlodipine
Annual per capita outpatient visit (mean)	27.21	32.60	22.11	24.79	27.38	25.04	19.73
Annual per capita hospital admission (mean)	0.49	0.39	0.38	0.55	0.37	0.48	0.32
Direction of outpatient flow (%)							
Tier 3 hospitals	31.96	31.03	32.24	36.08	32.71	29.38	57.32
Tier 2 hospitals	16.80	15.34	15.73	18.05	15.52	19.20	15.43
Tier 1 hospitals	48.26	50.96	49.59	42.57	49.36	48.32	26.11
Pharmacies	2.88	2.53	2.26	3.06	2.30	2.92	1.11
Others	0.10	0.14	0.18	0.23	0.11	0.18	0.03
Direction of inpatient flow (%)							
Tier 3 hospitals	54.04	59.97	56.10	56.68	58.56	50.25	77.98
Tier 2 hospitals	27.08	25.68	28.83	32.31	26.22	32.13	15.90
Tier 1 hospitals	18.18	13.94	13.44	9.79	13.60	15.88	5.50
Others	0.71	0.41	1.63	1.22	1.62	1.75	0.61

Abbreviation: GITs, gastrointestinal tablets.

gaps, continuous/single interval measure of medication acquisition, and continuous/single interval measure of medication gaps.[19] However, MPR is the most commonly used measure of treatment adherence.[18] MPR is used as a continuous variable or with appropriate justification, as a dichotomized variable.[18] However, it does not take gaps in refills into account and heavily depends on the denominator used during calculations (either number of days elapsed during the period or total study duration).[37] Hence, the MPR is not useful to evaluate nonadherence in case of premature terminations and gap in refilling.[37] In spite of these limitations, MPR has been used in various studies to assess treatment adherence as it is easy to calculate and interpret.[18,19] Previous studies have shown that the type of AHT drug prescribed significantly affects treatment adherence and persistence.[38–43] Among AHT agents, ACE inhibitors and CCBs are reported to have better treatment adherence and persistence compared with diuretics and β-blockers.[38–43] In a study carried out in Italian

Table 4 Factors Affecting MPR. Results of Multivariate Regression Analysis

Variables	Parameter estimation	Standard error	T value	P-value
Gender (male patients as control)	−0.0046	0.0024	−1.9	0.0573
Age (≤40 years as control)				
41–60 years	0.0776	0.0068	11.44	<0.0001
61–80 years	0.0999	0.0068	14.73	<0.0001
≥81 years	0.0912	0.0078	11.75	<0.0001
City level (prefecture level as control)				
Municipalities	0.0746	0.0042	17.72	<0.0001
Provincial capital	0.0040	0.0043	0.93	0.3516
Comorbidities				
Diabetes	0.0330	0.0027	12.18	<0.0001
Stroke	0.0112	0.0038	2.92	0.0035
Coronary artery disease	−0.0095	0.0030	−3.15	0.0016
Chronic renal diseases	0.0134	0.0074	1.81	0.0701
Peripheral vascular diseases	0.0215	0.0141	1.52	0.1290
Multidrug combination vs monotherapy	0.0221	0.0029	7.7	<0.0001
Visit to tertiary hospital	0.0821	0.0031	26.05	<0.0001
Number of hospitalizations	−0.0402	0.0030	−13.4	<0.0001
Average reimbursement ratio	0.1151	0.0042	27.05	<0.0001
Drug in the first prescription (benazepril alone as control)				
Nifedipine GITs	0.2829	0.0069	41.05	<0.0001
Amlodipine	0.1359	0.0065	20.78	<0.0001
Metoprolol	−0.1126	0.0068	−16.46	<0.0001
Valsartan	0.2553	0.0072	35.38	<0.0001
Indapamide	0.1024	0.0109	9.41	<0.0001
Valsartan/amlodipine FDC	0.2327	0.0118	19.74	<0.0001
Combination of two or more drugs	0.2825	0.0073	38.42	<0.0001

Abbreviations: FDC, fixed-dose combination; GITs, gastrointestinal tablets.

patients with HTN, it revealed a higher continuation rate in patients treated with ACE inhibitors (23.2%), ARBs (25.2%), and CCBs (23.9%) than in those treated with β-blockers and diuretics (11.2–11.8%).[39] Mancia et al have reported that the risk of discontinuation of AHT treatment was the lowest for ARBs (HR, 0.3; 95%CI, 0.29– 0.30], followed by ACE inhibitors (HR, 0.35; 95%CI, 0.51– 0.53), CCBs (HR, 0.52; 95% CI, 0.51– 0.53), and β-blockers (HR, 0.5; 95%CI, 0.53– 0.55) compared with diuretics.[44] Our results showing the highest treatment adherence for nifedipine GITs, and least treatment adherence for metoprolol, are in line with these previous observations.

Although replacement rate of drug was high in the indapamide group, treatment adherence for it was comparable to other classes of AHT drugs (Figure 2A–C). This is in contrast with the findings of Schulz et al, who reported the highest nonadherence for diuretics (66.3%) and the lowest for β-blockers (55.2%).[22] We speculate lower daily cost for indapamide treatment might have positively affected the adherence of patients with HTN to it.

In addition, our results showed that treatment adherence for AHT drugs is significantly affected by the level of the city with better adherence observed in patients receiving treatment in municipalities. The impact of city level on patients' adherence might be due to cost-efficient management services provided including health records, regular follow-ups and health education[45,46] as reported by a survey showing significant association between community management and AHT treatment adherence.[47] Furthermore, in our study, older age and presence of comorbidity positively affected treatment adherence, which is in line with the results of a study by Schulz et al showing lower nonadherence to AHT drugs in older patients (aged ≥65 years) than younger patients,[22] and other studies.[48,49] This highlights the need to improve health care for the younger population. In addition, our study showed lower adherence of females to treatment which is

in contrast with the findings of Wong et al.[29] Results from the China Health and Nutrition survey, which reported increased chances of receiving treatment (28.7%; 95%CI, 10.6– 46.7) among patients with health insurance also support our results showing the positive effect of the reimbursement ratio on AHT drug compliance.[50]

The strength of our study lies in the use of real-world data for the analysis, large sample size, and the accuracy of information available in the CHIRA database.

Our study had a few limitations. First, this was a retrospective study and so there are chances of bias in data selection and analysis. Second, the duration of this study was short, ie, one year due to which the treatment adherence observed could be higher than that of a study with longer duration. Third, 91.5% of the population included in the analysis was from the eastern region of China. Hence, the generalizability of these results to patients from central and western regions of China is limited. The analysis of treatment adherence was based on prescription information, and therefore, whether the drugs prescribed were consumed or not by the patients stays unclear. Hence, results should be interpreted carefully as there are chances of under- or overestimation of treatment adherence. Fourth, we could not evaluate the effect of treatment adherence on blood pressure control rate and health outcomes as the CHIRA database did not reflect information in this regard. Fifth, DDD was not suitable for MPR estimation of β-blockers. Finally, we did not examine other factors that can influence treatment adherence, such as social support, socioeconomic status of patients, and reminders for medicine intake.

Conclusion

Our results showed poor overall AHT treatment adherence among Chinese patients with HTN. Better reimbursement ratio, use of combination therapy and prescribing effective long-acting AHT drugs will help to improve treatment adherence, and hence HTN management, in China.

Ethics Approval and Informed Consent

The data from CHIRA database is available upon payment. As the study used patients deidentified data available from the CHIRA database, the study was exempted from Biomedical Ethics Committee of Peking University IRB approval with IRB communication no. IRB00001052-17012.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

Shanshan Li, Hua Xiao and Zhitao Liu are employees of Bayer Healthcare Company Limited (China). The authors declare that they have no other possible conflicts of interest in this work.

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