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# Comparison of Efficacies of Commonly Used Hypertension Treatment Modalities: A Retrospective Study of 1900 Participants in a Hypertension Clinic

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**Background:** Although various antihypertensive medications are available, some hypertensive patients have uncontrolled blood pressures, especially in the clinic. The aim of the present study was to compare the efficacies of various antihypertensive therapies in our hypertension (HTN) clinic (monotherapy vs. combination therapy, fixed-dose combination (FDC) versus free equivalent combination (FEC), and diuretics versus non-diuretics.

**Material/Methods:** In this retrospective study, patients at the HTN clinic of the Third Xiangya Hospital with primary hypertension were enrolled from June 2016 to February 2017. Data on participants' basic characteristics, blood pressure data, and treatment modalities were collected. The proportions of participants attaining target blood pressure after treatment with antihypertensive modalities were calculated and compared.





**Results:** Among 1900 participants, combination therapy had a better control efficacy than monotherapy ( $P < 0.0005$ ). When HTN was treated by 2 kinds of drugs, FEC was used much more frequently than FDC ( $P < 0.0005$ ). In grade 3 HTN, FDC had a higher control rate ( $P = 0.002$ ). If more than 2 kinds of drugs were used, FDC+OTHER had a slightly higher control rate in grade 2 and 3 (42.1% vs. 38.5%,  $P = 0.724$ ; 36.2% vs. 31.0%,  $P = 0.526$ , respectively). Therapies with diuretics had better control rates than those without diuretics (43.1% vs. 36.9%,  $P = 0.025$ ).

**Conclusions:** In our clinic, FEC was prescribed more often than FDC. When blood pressure is significantly elevated, especially at levels 2 or 3, FDC seems to have a better control rate than FEC. Therapies with diuretics controlled HTN more efficiently.

**MeSH Keywords:** **Drug Therapy, Combination • Hypertension • Retrospective Studies**

**Abbreviations:** **HTN** – hypertension; **ACEI** – angiotensin-converting enzyme inhibitor; **ARB** – angiotensin receptor blocker; **BB** –  $\beta$ -blocker; **CCB** – calcium channel blocker; **DU** – diuretic; **FDC** – fixed-dose combination; **FEC** – free equivalent combination

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## Background

Hypertension (HTN) is one of the major risk factors for the development of cardiovascular diseases [1], with a high prevalence affecting 972 million of the global adult population in 2000 which increased to 1.39 billion in 2010 and is expected to increase to 1.56 billion by 2025 [2,3].

Clinical management of HTN is one of the main public health challenges in primary care [4], in which 5 classes of antihypertensive drugs were recommended: angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), beta-blockers (BB), calcium channel blockers (CCB), and diuretics (DU) [5]. In many cases, blood pressure elevation is often multifactorial, making it complex to treat with a single agent; therefore, the use of multidrug combination therapy is recommended [6]. Recording to some research, drug combinations from the 5 classes are 5 times more effective than increasing the dose of a single drug [7].

With the discovery of new combination antihypertensive drugs, an emerging trend for prescribing and using fixed-dose combination (FDC) antihypertensive drugs have increased among clinicians and hypertensive patients due to its greater potential benefits, along with the simplification and adherence of the drug regimen, compared with free equivalent combination (FEC) antihypertensive drugs [8,9].

A number of studies showed that many hypertensive patients who are on antihypertensive therapy still have uncontrolled blood pressure [1,10–12]. There are many for this unfortunate result, including patient factors such as poor adherence and special pathogenesis, and physician factors such as priority prescriptions and unfamiliarity with some treatment combination [13]. This study focused on treatment modalities used in hypertensive patients in a busiest place HTN clinic.

The present study analyzed the usage rates and efficacies of monotherapy vs. combination therapy hypertensive treatment modalities in our HTN clinic, by comparing their rates of achieving target blood pressure in hypertensive patients. We also analyzed the usage rate and efficacies between FDC and FEC, and between diuretics and non-diuretics antihypertensive treatment modalities, by comparing their rates of achieving target blood pressure in hypertensive patients.

## Material and Methods

### Study population

This retrospective study included all voluntary patients with primary hypertension on antihypertensive medications and

regularly attending our HTN clinic of the Third Xiangya Hospital of Central South University for at least 3 months. The HTN clinic in our hospital was open from 8: 00 AM to 12: 00 PM on every Monday, Tuesday, and Thursday and from 2: 30 PM to 5: 30 PM on Friday. This study period was June 2016 to February 2017. We excluded patients who were under 18 years of age, defaulters, non-compliant with medications, no more than 3-month medication therapy, unavailable clinical medical records, and those with secondary HTN.

### Variables

The hypertensive treatment modality that a participant was on was regarded as the exposure statuses, including monotherapy and combination therapy, FDC and FEC, and diuretics and non-diuretics. We also recorded whether the target blood pressure was achieved.

### Definition of terms and diagnostic criteria

#### *Hypertension*

HTN was defined in accordance with published guidelines (Chinese Guidelines on Prevention and Control of HTN 2010) [14] as systolic or diastolic blood pressure  $\geq 140/90$  mmHg for more than 3 times in different days, or taking antihypertensive medication. HTN was classified as grade 1 (140–159/90–99 mmHg), grade 2 (160–179/100–109 mmHg) and grade 3 ( $\geq 180/110$  mmHg).

#### *Comorbidity*

Comorbidity was defined as the simultaneous presence of hypertension and other chronic diseases (e.g., chronic kidney disease, diabetes mellitus, and dyslipidemia), and cardiovascular disease (e.g., coronary arterial disease such as angina and myocardial infarction), heart failure, cardiomyopathy, arrhythmia, valvular heart disease, congenital heart disease, rheumatic heart disease, and stroke (ischemic or hemorrhagic).

#### *Target blood pressure*

Attaining, by a prescribed antihypertensive medication, a blood pressure of less than 140/90 mmHg in non-comorbid adult patients or less than 150/90 mmHg in patients above 65 years of age or less than 130/80 mmHg for patients with diabetes, renal disease and coronary heart disease was defined as target blood pressure [14].

#### *Blood pressure measurement*

Blood pressure was measured in accordance with Chinese Guidelines on Prevention and Control of HTN 2010 [14] using

an electronic sphygmomanometer (Omron-U15) by researchers in the hypertension clinic. The patients rested for at least 5 min before blood pressure measurement and sat during measurement. Blood pressure of both upper limbs were collected. The side with higher blood pressure was be measured again after 2 min. The average blood pressure was be calculated from these 2 results. If the 2 readings differed by at least 5 mmHg, a third measurement was made and the average blood pressure of the 3 readings was recorded, which was the assessment index for treatment outcome of this visit. Before the study began, all the researchers were professionally trained and examined by professor Weihong Jiang.

### Data collection

A structured questionnaire (Supplementary Table 1) was constructed to assess demographic characteristics (age, sex, height, weight), blood pressure and heart rate, and information related to hypertension, including family history of HTN, smoking history, duration of HTN, maximum blood pressure before 3 months ago, name of antihypertensive drugs taken in the last 3 months and comorbidities, some of which were collected from the clinic medical records. Maximum blood pressure before 3 months ago was used to divide patients into 3 groups depending on severity: grade I (140–159/90–99 mmHg), grade II (160–179/100–109 mmHg) and grade III ( $\geq$ 180/110 mmHg).

### Data analysis

Data analysis was performed in 2 levels: descriptive analysis and quantitative analysis. Descriptive analysis described the demographic and basic information of the study population in terms of sex distribution, mean age, hypertension distribution, heart rate, comorbidities, and risk factors, including HTN family history, smoking history, and basal metabolic index (BMI).

Quantitative analysis involved recording the number of participants in each of the 3 groups (I, II, and III) that achieved the target blood pressure using any of the 2 hypertension treatment modalities: monotherapy or combination therapy. Secondly, the combination therapy modality group was further split into 4 subgroups: fixed-dose combination (FDC), free equivalent combination (FEC=2 drugs), free equivalent combination (FEC  $\geq$  3 drugs), and fixed-dose combination plus other (FDC+OTHER). Therapies with diuretics and non-diuretics were also sub-grouped. Efficacies among these subgroups were again compared among one another.

Data were recorded in Microsoft Excel Home edition 2016 spreadsheets and exported to SPSS version 23.0 (SPSS, Inc., Chicago, USA) for analysis. Continuous variables are presented as mean $\pm$ standard deviation (SD) and categorical variables as percentages. The chi-square test was used to test differences

between enumeration data, and the *t* test was used to test measurement data. A P-value of less than 0.05 was considered significant. The power of the test was calculated in the control rate in every subgroup [15,16].

### Ethics approval

The study approval permit was obtained on 31 October 2014 with the protocol number of NO: 2014-S163 from The IRB (Institutional Review Board) of the Third Xiangya Hospital, Central South University, headed by professor Jiexiang Lu. This study was conducted in accordance with the Helsinki Declaration. Details about the objective and the aim of the study were explained to the participants, and informed consent was obtained from all of them.

## Results

### Baseline characteristics

Table 1 summarizes the baseline characteristics of the study population. Of 1900 included participants, the mean age was 60.1 $\pm$ 12.0 years, and 51.9% were females. The mean heart rate was 81.0 $\pm$ 14.0 bpm (beats per minute). Hypertension distribution increased with increasing age ( $P<0.0005$ ). More than half of the participants were  $\geq$ 60 years old and only 5.3% were under 39 years old. Among the participants, there were more with lower BMI than those with higher BMI (58.1% vs. 6.1%,  $P<0.0005$ ).

Patients with smoking history and comorbidity were not more likely to have HTN; rather, the reverse was found (21.7% vs. 78.3%,  $P<0.0005$  and 37.8% vs. 62.2%,  $P=0.007$ ). No significant differences in distribution were found among different HTN grades and family histories.

Distribution of different antihypertensive therapy are shown in Table 2. Monotherapy (45.6%) and FEC (2 drugs) (30.3%) were used more than others for HTN treatment. The rates of use of FDC, FEC ( $\geq$ 3 drugs), and FDC+OTHER were 5.8%, 9.6%, and 8.7%, respectively.

### Distribution and control rate of monotherapy drugs

Among 866 participants, there were 548 using CCB for HTN treatment, which was mostly prescribed in various HTN levels when HTN was treated by only one kind of drug. BB and DU were comparatively less prescribed (42/866 and 52/866, respectively). Although there was some diversity in prescription, the control rates achieved with those drugs were almost the same (about 30–45% in average). Only in BB, it seems that the control rate was a little higher than with the other 4 drugs (64.3%) (Table 3). The test power of control rate was all  $>90\%$ .

**Table 1.** Characteristics of participants by sex.

Characteristics	Male	Female	Total	P Value
Number of participants (n,%)	914 (48.1)	986 (51.9)	1900 (100)	0.099
Age (years, mean±SD)	59.4±12.8	60.9±11.1	60.1±12.0	0.006
Heart Rate (bmp, mean±SD)	80.5±14.7	81.5±13.3	81.0±14.0	0.139
Age group (n,%)				
18–39 years	68 (3.6)	32 (1.7)	100 (5.3)	
40–59 years	362 (19.1)	398 (20.9)	760 (40.0)	<0.0005
≥60 years	484 (25.4)	556 (29.3)	1040 (54.7)	
Previous HTN grade (n,%)				
Grade 1	174 (9.2)	212 (11.1)	386 (20.3)	
Grade 2	478 (25.1)	484 (25.5)	962 (50.6)	0.290
Grade 3	262 (13.8)	290 (15.3)	552 (29.1)	
BMI (kg/m <sup>2</sup> , mean±SD)	25.2±3.18	24.0±3.2	24.6±3.26	
<25(n, %)	464 (24.4)	640 (33.7)	1104 (58.1)	
25–30 (n, %)	386 (20.3)	294 (15.5)	680 (35.8)	<0.0005
≥30 (n, %)	64 (3.4)	52 (2.7)	116 (6.1)	
Family History (n, %)				
Absent	420 (22.1)	466 (24.5)	886 (46.6)	
Present	494 (26.0)	520 (27.4)	1014 (53.4)	0.581
Smoking History (n, %)				
Smoker	382 (20.1)	30 (1.6)	412 (21.7)	
Non-smoker	532 (28.0)	956 (50.3)	1488 (78.3)	<0.0005
Comorbidity (n%)				
Absent	540 (28.4)	642 (33.8)	1182 (62.2)	
Present	374 (19.7)	344 (18.1)	718 (37.8)	0.007

HTN – hypertension. Grade 1: 140–159/90–99 mmHg; Grade 2: 160–179/100–109 mmHg; Grade 3: ≥180/110 mmHg.

**Table 2.** Distribution of different antihypertensive therapy.

Antihypertensive therapy	Number of participants (%)
Monotherapy	866 (45.6)
FDC	110 (5.8)
FEC (2 drugs)	575 (30.3)
FEC (≥3 drugs)	183 (9.6)
FDC+OTHER	166 (8.7)
Total	1900 (100.0)

FDC – fixed dose combination; FEC – free Equivalent combination.

**Distribution and control rate between monotherapy and combination therapy**

In grade 1 HTN, monotherapy was used more frequently than combination therapy (246/386 vs. 140/386, P<0.0005). In contrast, in grade 2 and 3 HTN, combination therapy was used more frequently (518/962 vs. 444/962, P=0.019 and 376/552 vs. 176/552, P<0.0005, respectively). In grade 1 HTN, monotherapy had a higher control rate (60.2% vs. 48.6%, P=0.033), while in grade 2 and 3 HTN, combination therapy had a higher control rate (43.6% vs. 31.5%, P<0.0005 and 33.0% vs. 15.9%, P<0.0005) (Table 4).

**Table 3.** Distribution and HTN control rate of monotherapy drugs by grade of HTN.

	Grade 1 HTN		Grade 2 HTN		Grade 3 HTN		Total	
	Distribution	Control rate	Distribution	Control rate	Distribution	Control rate	Distribution	Control rate
ACEI	24	12 (50.0)	40	11 (27.5) <sup>a</sup>	14	2 (14.3)	78	25 (32.1) <sup>a</sup>
ARB	34	21 (61.8)	86	22 (25.6) <sup>a</sup>	26	2 (7.7)	146	45 (30.8) <sup>a</sup>
BB	18	11 (61.1)	20	14 (70.0) <sup>b</sup>	4	2 (50.0)	42	27 (64.3) <sup>b</sup>
CCB	164	98 (59.8)	262	80 (30.5) <sup>a</sup>	122	18 (14.8)	548	196 (35.8) <sup>a</sup>
DU	6	6 (100.0)	34	13 (38.2) <sup>a,b</sup>	12	4 (33.3)	52	23 (44.2) <sup>a,b</sup>
<b>Total</b>	<b>246</b>	<b>148 (60.2)</b>	<b>442</b>	<b>140 (31.7)</b>	<b>178</b>	<b>28 (15.7)</b>	<b>866</b>	<b>316 (36.5)</b>
P value	<0.0005	0.281 <sup>#</sup>	<0.0005	0.003 <sup>#</sup>	<0.0005	0.102 <sup>#</sup>	<0.0005	0.001 <sup>#</sup>

HTN – hypertension. Control rate was shown in number (percentage). Power was calculated for Control Rate. <sup>#</sup> Power>90%.

<sup>a, b</sup> Significant difference was shown in different superscript.

**Table 4.** Distribution and HTN control rate of different therapy by grade of HTN.

Antihypertensive therapy	Grade 1 HTN		Grade 2 HTN		Grade 3 HTN		Total	
	Distribution	Control rate	Distribution	Control Rate	Distribution	Control Rate	Distribution	Control Rate
<b>Monotherapy and combination therapy</b>								
Monotherapy	246	148 (60.2)	444	140 (31.5)	176	28 (15.9)	866	316 (36.5)
Combination therapy	140	68 (48.6)	518	226 (43.6)	376	124 (33.0)	1034	418 (40.4)
Total	386	216 (56.0)	962	366 (38.0)	552	152 (27.5)	1900	734 (38.6)
P value	<0.0005	0.033 <sup>1</sup>	0.019	<0.0005 <sup>#</sup>	<0.0005	<0.0005 <sup>#</sup>	<0.0005	0.080 <sup>2</sup>
<b>FDC and FEC (2 drugs) therapy</b>								
FDC	12	6 (50.0)	70	33 (47.1)	28	16 (57.1)	110	55 (50.0)
FEC (2 drugs)	92	50 (54.3)	313	135 (43.1)	170	44 (25.9)	575	229 (39.8)
Total	104	56 (53.8)	383	168 (43.9)	198	60 (30.3)	685	284 (41.5)
P value	<0.0005	1.000 <sup>#</sup>	<0.0005	0.595 <sup>#</sup>	<0.0005	0.002 <sup>#</sup>	<0.0005	0.057 <sup>3</sup>
<b>FDC+OTHER and FEC (≥3 drugs) therapy</b>								
FDC+OTHER	15	4 (26.7)	57	24 (42.1)	94	34 (36.2)	166	62 (37.3)
FEC (≥3 drugs)	21	8 (38.1)	78	30 (38.5)	84	26 (31.0)	183	64 (35.0)
Total	36	12 (33.3)	135	54 (40.0)	178	60 (33.7)	349	126 (36.1)
P value	0.405	0.721 <sup>##</sup>	0.085	0.724 <sup>#</sup>	0.500	0.526 <sup>##</sup>	0.392	0.657 <sup>#</sup>

FDC – fixed dose combination; FEC – free equivalent combination; HTN – hypertension. Control rate was shown in number (percentage). Power was calculated for Control Rate. <sup>#</sup> Power >90%; <sup>##</sup> Power >80%. <sup>1</sup> Power=59.69%; <sup>2</sup> Power=58.15%;

<sup>3</sup> Power=50.96%.



**Table 5.** Distribution and HTN control rate in therapy with or without diuretic.

Antihypertensive therapy	Diuretic used		Non-Diuretic used		P value
	Distribution	Control rate	Distribution	Control rate	
Monotherapy	52	23 (44.2)	814	293 (36.0)	0.232
FEC (2 drugs)	46	20 (43.4)	529	209 (39.5)	0.598
FDC	97	49 (50.5)	13	6 (46.2)	0.768
FEC (≥3 drugs)	48	18 (37.5)	135	46 (34.1)	0.669
FDC+OTHER	154	61 (39.6)	12	1 (8.3)	0.033*
Total	397	171 (43.1)	1503	555 (36.9)	0.025*

Distribution was shown in number. Control rate was shown in number (percentage). P-value was for comparing control rate in the same antihypertensive therapy with or without diuretic. \* P<0.05 was considered significant. FDC – fixed dose combination; FEC – free equivalent combination; HTN – hypertension.

### Distribution and control rate between FDC and FEC (2 drugs) therapy

In different levels of HTN, if HTN was treated by 2 kinds of drugs, FEC was used much more frequently than FDC (575/685 vs. 110/685 in total, P<0.0005). In grade 1 and 2 HTN, FDC and FEC had a similar control rate of HTN, but in grade 3 HTN, FDC had a higher control rate (57.1% vs. 25.9%, P=0.002) (Table 4).

### Distribution and control rate between FDC+OTHER and FEC (≥3 drugs) therapy

In different levels of HTN, if HTN was treated by more than 2 kinds of drugs, FDC+OTHER and FEC therapy had almost the same utilization rate (166/349 vs. 183/349 in total, P=0.392). These 2 therapies did not show significant differences in control rate in any level of HTN, although it seems FEC had a slightly higher control rate in grade 1 HTN (38.1% vs. 26.7%, P=0.721) and FDC+OTHER had a slightly higher control rate in grade 2 and 3 (42.1% vs. 38.5%, P=0.724 and 36.2% vs. 31.0%, P=0.526, respectively) (Table 4).

### Distribution and HTN control rate in therapy with or without diuretics

Among 1900 patients, there were 397 patients (20.9%) who used diuretics for antihypertension altogether in single drug and multiple drugs, in which FDC (including FDC+OTHER) accounted for a large portion. In all subgroups, the therapies with diuretics had a higher control rate than those without diuretics, especially in the FDC+OTHER group (39.6% vs. 8.3%, P=0.033) and total (43.1% vs. 36.9%, P=0.025) (Table 5).

## Discussion

Our study innovatively observed the population of hypertensive patients in an HTN clinic. A number of similar studies have previously been conducted on such inpatients [17–19], but this study focused on a greater number of patients in one of the busiest places, HTN clinics, making this real-world research that accurately reflects the situation of HTN patients. Our study found that of all 5 first-line antihypertensives, CCB was the most frequently used, followed by FEC. FDC was used less frequently than FEC and CCB. Despite these differences, efficacies were very similar at different levels of HTN, except for FDC, which was better in higher grades of HTN.

Despite an insignificant association with sex, HTN was associated with age – old age was more associated with hypertension than younger age – which agrees with other studies [1,10]. Furthermore, interestingly, we observed that the higher BMI and more smoking were associated with lower proportions of HTN. We also found that HTN was more distributed in non-comorbid than in comorbid patients. These 2 findings contradict previous reports on these associations. This can be explained by the limited scope of this study, which only included hypertensive patients attending a hypertensive clinic. Hypertensive patients with more complications were not more likely to attend a hypertensive clinic, but tended to seek care at specialized clinics, depending on their complications [20,21], such as heart clinics for coronary heart disease and heart failure or pulmonology clinics for chronic obstructive pulmonary disease (COPD) resulting from HTN complications. This falsely suggests that HTN is less common in participants with higher BMI, with smoking habit, and with no comorbidity.

Single antihypertensive drug prescription accounted for nearly half of all antihypertensive prescriptions in all hypertensive grades in our study. Recent research shows that drug

combinations have a greater cardiovascular-protective effect than monotherapy modalities in initial treatment [22], especially when blood pressure is  $>150/95$  mmHg [23]. This means that many patients in our clinic might not be getting the most effective treatment for their blood pressure because they are receiving a single drug instead of 2 antihypertensive drugs [24].

Other research has shown CCB monotherapy is more often prescribed as compared to other antihypertensives [25,26]. Our research verified this result in our HTN clinic. This could be due to its superior prognostic effects [27] and wider indications [28,29] as compared to other antihypertensives; for example, ACEI/ARB can affect renal function, BB can reduce heart rate and worsen heart failure, and can elevate uric acid levels. In our study, the efficacies were very similar in all antihypertensive treatment modalities, except for BB, whose efficacy was slightly better than the rest, perhaps because pharmacologically it has 2 sites of action – on blood vessels and on the heart. Another reason could be its sympathetic depression effect, alleviating patients' anxiousness when they visit doctors, referred to as "white-coat hypertension" [30].

Regarding combination treatment modalities, FEC (involving 2 drugs) was significantly more prescribed than FDC, a finding that is not in accordance with some other studies' conclusions [9,31,33]. Combination treatment modality – FEC (involving 2 drugs) – was also associated with better compliance than FDC, a finding that could partly be explained by some patients' erroneous belief that "more pills create more effect". Another reason is that it is more convenient for many physician internists to adjust the treatment modality in 2 different pills. Further research is needed to investigate FEC (involving 2 drugs) prescriptions compared to other treatment modalities.

In combination therapies involving 3 or more antihypertensive drugs, there was no significant difference in the prescription choices between FDC+OTHER versus FEC (involving  $\geq 3$  drugs). This could be due to the myth that 2 pills or 3 pills are "just equally effective enough". That is to say, for both patients and doctors, prescribing more than 1 pill for HTN seems to be as convenient as prescribing just 1 pill. In reality, both FDC+OTHER and FEC (involving  $\geq 3$  drugs) showed similar blood pressure control efficacies in our research.

We found that FDC efficacy was significantly higher than that of FEC (involving 2 drugs) for treatment of Grade 3 HTN. In the population with Grade 2 and Grade 3 HTN, the efficacy of FDC(+OTHER) was still higher than that of FEC (involving  $\geq 2$  drugs), although the difference was not statistically significant. Although FEC was prescribed more than FDC, the efficacy of FDC was slightly higher than that of FEC, especially when blood pressure was significantly elevated, which is an interesting phenomenon. This could be explained by the fact

that FDC involves more evidence-based combinations of antihypertensives that are pharmacologically compatible [34] to reduce some adverse effects and more than double the benefits as compared to FEC, in which a physician can freely combine any antihypertensives of their choice. Also, FDC might have better adherence and compliance for hypertensive patients than FEC in some cases [9,35].

In recent years there has been controversy about whether to prescribe FDC or FEC for patients with hypertension. Although the guidelines recommended more use of FDC, an editorial published in November 2017 in JAMA questioned whether FDC is suitable for most patients with hypertension [36]. In fact, the specific conditions of each hypertension patient are different (e.g., different diet, weight, amount of exercise), so individualized antihypertensive therapy strategies are desperately needed. FEC, but not FDC, may be the best individualized antihypertensive scheme in clinical practice. Compared with the FDC recommended in the current guidelines, the free combination of drug delivery may be more feasible in clinical practice. One reason is that, compared to FDC, with FEC it is easy to adjust the time and dose of drug delivery and ensure the effectiveness and sustainability of the 24-hour effect [37]. Another reason is that free-combination drug delivery matches the body's chronobiology [38] and can control blood pressure more effectively and smoothly, reducing adverse reactions and improving patients' compliance [39]. On the contrary, it is difficult to adjust the dosage of FDC because it is hard to judge which drug in it caused adverse reactions in clinical practice [39]. A nested case-control analysis showed that FDC significantly increased the occurrence of adverse events such as hypotension and syncope [40], while with FEC one can gradually adjust the dosage of drugs so that the adverse effects caused by the increase of dose can be avoided [37]. Evidence from a 4-year follow-up study showed that patients with initial free combination therapy had better compliance [41], and a study from Japan showed that patient compliance with FDC was not superior to that of FEC [42]. All the conclusions above are in accordance with some of ours, that is, FDC may not be better than FEC [43]. Further research is needed on the mechanism underlying the observed effects. We suggest that FDC be prescribed in the patients following the guidelines, especially for patients with higher blood pressure.

It is fascinating that therapies with diuretics have a more effective control rate than those without diuretics. Especially in multiple drugs, the superiority of diuretics stands out. Some researchers found that resistant hypertension was related to retaining salt and water and that the renin-aldosterone system was involved in blood pressure control [13,44]. Salt intake plays a very important role in hypertension in China. Research shows that instead of choosing drugs blindly, it is important in patients with resistant hypertension to measure stimulated

plasma renin and aldosterone to identify the best therapy for each patient [44,45].

This study had several sources of bias. The population included in this study, although representative of the general population in the real world, had only mild illnesses seen at clinics and not the severe illnesses of patients admitted in the wards. Furthermore, although the total number is quite large, with the subdivision into groups, the number of some subgroups is relatively small, leading to the low power of some individual subgroups. Therefore, further studies are needed to expand the survey population, including other outpatient clinics and departments and patients with more serious conditions to fully represent the association of various antihypertensive regimens in HTN and their antihypertensive effect.

## Conclusions

Appropriate antihypertensive treatment modality – i.e., monotherapy or combination therapy (including FEC or FDC, diuretics or non-diuretics) – is essential for achieving adequate efficacy in treatment of hypertension to avoid HTN complications. Our study observed that monotherapy with CCB was more widely used than the other 4 first-line antihypertensive drugs, despite similar blood pressure control efficacy. In the combination therapy modality, FEC was more often prescribed by physicians in treating hypertension than was FDC. However, with hypertension grades II and grade III, FDC seemed to have better efficacy than FEC. Therapies with diuretics have better control rates than those without diuretics. We suggest that more FDC be prescribed for grade II and III hypertensive patients since it is more effective and FEC could be more associated with non-evidence-based prescriptions, leading to unfortunate risks such as accidental drug duplications or drug-drug interactions [43], and measuring stimulated plasma renin and aldosterone be conducted when necessary.

## Conflicts of interest

None.

## Supplementary Data

Supplementary Table 1. Research questionnaire.

Research Questionnaire		
Age:	Gender:	
Hight:	Weight:	
BP 1:	HR 1:	
BP 2:	HR 2:	
BP 3:	HR 3:	
Average BP:	Average HR:	
Family history of HTN	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Smoking history	Yes <input type="checkbox"/>	No <input type="checkbox"/>
History of HTN		
Duration of HTN:		
➤ Maximum blood pressure before 3 months ago:		
➤ Current HTN drugs in 3 months:		
➤ Comorbidities:		

HTN – hypertension; BP – blood pressure; HR ,– heart rate.



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