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Original Article

Clinical efficacy and psychological benefits of combination therapy in elderly patients with hypertension

Putian Zhang[1*], Teng Cui[2*], Xiaojie Ye[2], Miao Lu[3]

[1]Class of 2022, Nanjing Medical University, Nanjing 211166, Jiangsu, China; [2]Department of Geriatric, The Second People's Hospital of Kunshan, Kunshan 215300, Jiangsu, China; [3]Department of Geriatrics Medicine, Jiangsu Province Hospital (The First Affiliated Hospital with Nanjing Medical University), Nanjing 210029, Jiangsu, China. [*]Equal contributors.

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Abstract: Objective: To investigate the effects of different antihypertensive agents on psychiatric symptoms and blood pressure control in elderly patients with hypertension. Methods: This retrospective study included 300 elderly patients with hypertension. Patients were categorized based on their antihypertensive medication regimen: divided into the monotherapy group (n=70) and combination therapy group (n=230), with each further subdivided by medication type. The monotherapy group comprised angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) (n=10), calcium channel blockers (CCBs) (n=33), β-blockers (β-Bs) (n=22), and diuretic (n=5) subgroups. The combination therapy group included ACEIs/ARBs + diuretic (n=12), CCBs + diuretic (n=9), β-Bs + diuretic (n=21), ACEIs/ARBs + CCBs (n=36), CCBs + β-Bs (n=69), ACEIs/ARBs + β-Bs (n=26), and ACEIs/ARBs + β-Bs + CCBs (n=57) subgroups. Blood pressure, anxiety, depression, and sleep quality were evaluated before and after 8 weeks of treatment. Multivariate logistic regression was used to identify factors associated with poor treatment efficacy. Results: The Combination therapy group achieved superior blood pressure control compared with the monotherapy group (75.65% vs. 47.14%). Both the ACEIs/ARBs and the ACEIs/ARBs + CCBs groups had significantly improved anxiety, depression, and sleep quality (all $P<0.05$). In contrast, the β-Bs and β-Bs + diuretics groups had aggravated psychiatric symptoms. The incidence of adverse events was comparable among groups (all $P>0.05$). After adjustment for confounding factors, combination therapy remained a protective factor for treatment efficacy ($P<0.05$). Conclusion: Combination therapy is more effective for blood pressure control in elderly patients with hypertension. ACEIs/ARBs, alone or combined with CCBs, alleviate psychiatric symptoms, whereas β-blockers, especially when combined with diuretics may exacerbate them. The efficacy advantage of combination therapy is independent of potential confounders.

Keywords: Antihypertensive drugs, elderly hypertension, mental symptoms, efficacy comparison, influencing factors analysis

Introduction

Globally, hypertension is a major risk factor for cardiovascular and chronic kidney diseases [1], predominantly affecting middle-aged and elderly individuals. Elderly patients with hypertension often present with multiple comorbidities, among which the prevalence of cognitive impairment, depression, anxiety, and sleep disorders is markedly higher than in the general population [2, 3]. Clinical studies have shown that elderly hypertensive patients with concomitant psychiatric symptoms have more than a 40% higher risk of cardiovascular events compared to those without such symptoms [4]. Therefore, in the antihypertensive management of elderly patients, drug selection should not only emphasize the effectiveness of blood pressure control but also consider the potential effects on psychiatric symptoms. However, controversy remains regarding the influence of different antihypertensive agents on blood pressure and psychiatric outcomes, and most existing studies have focused on single-drug evaluations rather than systematic comparisons [5-7]. In particular, the balance between antihypertensive efficacy and improvement in psychiatric symptoms across various drug classes has not

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been clearly defined in elderly populations. This study aimed to investigate the effects of different antihypertensive agents on blood pressure control and psychiatric symptoms (depression, anxiety, and sleep quality) in elderly hypertensive patients and to identify factors associated with poor blood pressure control. The findings are expected to provide a basis for individualized pharmacological strategies and to optimize comprehensive management emphasizing both "blood pressure reduction and mental stabilization".

Information and methods

General information

A retrospective cohort of 300 elderly patients with hypertension who were admitted to The Second People's Hospital of Kunshan between January 2024 and May 2025 was included in this study. This study was approved by the Ethics Committee of The Second People's Hospital of Kunshan.

Inclusion criteria: (1) patients meeting the diagnostic criteria for elderly hypertension, defined as age ≥65 years and persistent elevated blood pressure (systolic blood pressure [SBP] ≥140 mmHg and/or diastolic blood pressure [DBP] ≥90 mmHg on three or more separate occasions) in the absence of prior antihypertensive drug use [8]; (2) primary hypertension; (3) continuous use of the same class of antihypertensive medication or regimen for ≥8 weeks; (4) complete clinical data, including demographic information, medication records, laboratory test results, and baseline and follow-up blood pressure values; (5) normal cognitive and communication abilities.

Exclusion criteria: (1) secondary hypertension; (2) a history of psychiatric disorders (including depression, anxiety, schizophrenia, or dementia); (3) recent use of antidepressants, antipsychotics, or sedative-hypnotic drugs; (4) severe neurological disorders; (5) irregular use of antihypertensive medication (adherence <80%, assessed by prescription refill frequency); (6) comorbid conditions that may affect blood pressure (e.g., pheochromocytoma, renal artery stenosis); (7) severe hepatic or renal insufficiency; (8) tumors or hematologic malignancies.

Information collection

Patient information was obtained from the hospital's electronic medical records and laboratory information systems and included the following:

(1) General information: gender, age, body mass index (BMI), smoking and alcohol history, disease duration, hypertension grade, comorbidities (diabetes mellitus, coronary artery disease, chronic kidney disease, hyperlipidemia), type of antihypertensive drug, and treatment regimen.

Smoking was defined as current smoking or cessation within the past 5 years. Alcohol consumption was defined as the intake of ≥1 alcoholic beverage per week during the past year in individuals who were not currently abstinent.

(2) Blood pressure measurements: seated SBP and DBP values were recorded before treatment and after 8 weeks of treatment.

(3) Psychological symptom assessment: Psychological symptoms were evaluated using the Generalized Anxiety Disorder-7 (GAD-7), Patient Health Questionnaire-9 (PHQ-9), and Pittsburgh Sleep Quality Index (PSQI) before treatment and 8 weeks after treatment.

GAD-7: seven items scored from 0-3 based on symptom frequency in the past 2 weeks, yielding a total score of 0-21. Higher scores indicate more severe anxiety: 0-4 (none), 5-9 (mild), 10-14 (moderate), 15-21 (severe) [9].

PHQ-9: nine items scored 0-3 according to symptom frequency, with a total score of 0-27. Higher scores denote more severe depression: 0-4 (none), 5-9 (mild), 10-14 (moderate), 15-19 (moderately severe), 20-27 (severe) [10].

PSQI: 19 self-rated items grouped into seven components - subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of hypnotics, and daytime dysfunction. Each component is scored 0-3, with a total score of 0-21. Higher scores indicate poorer sleep quality; a PSQI score >7 indicates a clinically significant sleep disorder [11].

All scale data (GAD-7, PHQ-9, PSQI) were collected and entered by trained medical staff blinded to the group assignments.

(4) Inflammatory indicators: Neutrophil count (NEUT), lymphocyte count (LYMPH), monocyte count (MONO), and platelet count (PLT) were collected. The systemic immune-inflammation index (SII) and pan-immune-inflammation va-

lue (PIV) were calculated using the following formulas: SII = (PLT × NEUT) ÷ LYMPH; PIV = (NEUT × PLT × MONO) ÷ LYMPH.

(5) Carotid ultrasound findings: Carotid plaques and the degree of carotid artery stenosis (mild <50% vs. moderate-to-severe ≥50%) were assessed [12].

Plaque was defined as a focal structure protruding into the lumen >0.5 mm, or a localized increase in carotid intima-media thickness (CIMT) >1.5 mm or exceeding 50% of the adjacent intima-media thickness, identified on longitudinal and cross-sectional scans [13]. The severity of stenosis was classified according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria [14].

(6) Adverse events: Adverse reactions were recorded and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [15]: Grade 1 (mild): discomfort without interference in daily activities; no medical intervention required; Grade 2 (moderate): symptoms interfere with daily activities; medical intervention may be required; Grade 3 (severe): inability to work or significant interference with daily function, requiring medical intervention.

Drugs and subgroups

The antihypertensive drugs used in this study included angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), diuretics, and β-blockers (β-Bs). The most commonly prescribed drugs in each category were as follows: (1) ACEIs: Captopril Tablets (Beijing Shuguang Pharmaceutical Co., Ltd., National Drug Approval No. H11020833); (2) ARBs: Losartan Potassium Tablets [Merck (China) Co., Ltd., National Drug Approval No. H2017-1246]; (3) CCBs: Amlodipine Besylate Tablets (Pfizer Pharmaceuticals Limited, National Drug Approval No. H20093660); (4) Diuretics: Hydrochlorothiazide Tablets (Renhetang Pharmaceutical Co., Ltd., National Drug Approval No. H37020788); (5) β-Bs: Metoprolol Tablets (AstraZeneca AB, Sweden, National Drug Approval No. H20100098).

Patients were divided into the monotherapy group (n=70) and the combination therapy group (n=230) according to the type of antihypertensive regimen used. The combination therapy group included patients receiving two or more drugs. Further subgroup classification was based on specific drug combinations: ACEIs/ARBs + diuretic (n=12), CCBs + diuretic (n=9), β-Bs + diuretic (n=21), ACEIs/ARBs + CCBs (n=36), CCBs + β-Bs (n=69), ACEIs/ARBs + β-Bs (n=26), and ACEIs/ARBs + β-Bs + CCBs (n=57).

Observation indicators

(1) The change in sitting DBP after 8 weeks of treatment compared with baseline (DBP at 4 and 8 weeks minus baseline DBP); (2) The change in sitting SBP after 8 weeks of treatment compared with baseline (SBP at 8 weeks minus baseline SBP); (3) The effective rate after 8 weeks of treatment, defined as the proportion of patients achieving sitting SBP <140 mmHg and DBP <90 mmHg, or a reduction of ≥20 mmHg in SBP and ≥10 mmHg in DBP from baseline; (4) Changes in anxiety, depression, and sleep quality scores after 8 weeks of treatment; (5) Safety indicators (adverse events); (6) Factors influencing poor efficacy.

Statistical analysis

Statistical analyses were performed using SPSS version 23.0. Normally distributed continuous variables were expressed as mean ± standard deviation ($\bar{x}\pm sd$), and compared between groups using the independent-samples t-test. Non-normally distributed variables were expressed as median (P25, P75) and compared using non-parametric tests. Categorical variables were presented as frequencies (n) and percentages (%), and intergroup differences were analyzed using the chi-square test or Fisher's exact test as appropriate. Multivariate logistic regression analysis was applied to identify independent factors associated with poor treatment efficacy. A P value <0.05 was considered statistically significant.

Results

Comparison of baseline characteristics between monotherapy and combination therapy groups

There were no statistically significant differences in gender, age, BMI, place of residence, edu-

Table 1. Baseline data [$\bar{x}$±s, M (P25, P75), n (%)]

Data	Monotherapy group (n=70)	Combination therapy group (n=230)	t/z/x^2 values	*P* values
Gender			0.441	0.507
Male	43 (61.43)	131 (56.96)		
Female	27 (38.57)	99 (43.04)		
Age	72.69±5.07	73.70±5.24	1.422	0.156
BMI (kg/m^2)	26.24±3.54	25.98±2.52		
Place of residence			0.065	0.799
Rural area	25 (35.71)	86 (37.39)		
City	45 (64.29)	144 (62.61)		
Course of disease	11.00 (7.00, 14.25)	11.00 (7.00, 16.00)	0.419	0.675
History of smoking	13 (18.57)	49 (21.30)	0.244	0.621
History of alcohol consumption	10 (14.29)	42 (18.26)	0.592	0.442
Diabetes mellitus	11 (15.71)	50 (21.74)	1.203	0.273
Coronary heart disease	25 (35.71)	79 (34.39)	0.044	0.833
Complicated chronic kidney disease	8 (11.43)	32 (13.91)	-	0.592
Combined with hyperlipidemia	8 (11.43)	47 (20.43)	-	0.059
Educational level			0.044	0.834
Junior high school and below	34 (48.57)	115 (50.00)		
High school and above	36 (51.43)	115 (50.00)		
Baseline SBP (mmHg)	152.64±10.27	150.47±9.67	1.619	0.106
Baseline SDP (mmHg)	97.53±5.76	96.58±4.67	1.401	0.162
Baseline GAD-7 score	6.41±2.04	6.69±2.00	1.009	0.314
Baseline PHQ-9 score	6.99±2.69	7.25±2.59	0.735	0.463
Baseline PSQI score	8.37±2.72	8.43±2.29	0.164	0.870
Baseline anxiety level			0.733	0.693
None	13 (18.57)	35 (15.22)		
Mild	52 (74.29)	173 (75.22)		
Moderate/Severe	5 (7.14)	22 (9.57)		
Baseline depression level			0.002	0.962
None/Mild	58 (82.86)	190 (82.61)		
Moderate/Severe	12 (17.14)	40 (17.39)		
Baseline sleep disorder level			0.087	0.768
No significant sleep disorder	26 (37.14)	81(35.22)		
With significant sleep disorder	44 (62.86)	149 (64.78)		
Degree of carotid artery stenosis			4.288	0.117
Normal	42 (60.00)	167 (72.61)		
Mild stenosis	17 (24.29)	35 (15.22)		
Moderate to severe stenosis	11 (15.71)	28 (12.17)		
Carotid plaques were present	29 (41.43)	87 (37.83)	0.294	0.588
Carotid plaque area (mm^2)	0.00 (0.00, 30.23)	0.00 (0.00, 24.72)	0.623	0.533

Notes: BMI: body mass index, SBP: systolic blood pressure, SDP: diastolic blood pressure, GAD-7: Generalized Anxiety Disorder scale, PHQ-9: Patient Health Questionnaire-9, PSQI: Pittsburgh Sleep Quality Index scale.

cational level, comorbidities, or baseline blood pressure between the monotherapy and combination therapy groups (all P>0.05; **Table 1**). Likewise, baseline anxiety, depression, and sleep-quality scores did not differ significantly either within the monotherapy group, within the combination therapy group, or across all groups (all P>0.05; **Table 2**).

Table 2. Comparison of baseline anxiety, depression, and sleep disorder levels among groups [n (%)]

Group	Baseline anxiety level			Baseline depression level		Baseline sleep disorder level	
	None	Mild	Moderate/ Severe	None/ Mild	Moderate/ Severe	No significant sleep disorder	With significant sleep disorder
Monotherapy group (n=70)							
ACEIs/ARBs (n=10)	1 (10.00)	8 (80.00)	1 (10.00)	9 (90.00)	1 (10.00)	3 (30.00)	7 (70.00)
CCBs (n=33)	7 (21.21)	23 (69.70)	3 (9.09)	25 (75.76)	8 (24.24)	11 (33.33)	22 (66.67)
β-Bs (n=22)	4 (18.18)	17 (77.27)	1 (4.55)	19 (86.36)	3 (13.64)	10 (45.45)	12 (54.55)
Diuretics (n=5)	1 (20.00)	4 (80.00)	0 (0.00)	5 (100.00)	0 (0.00)	2 (40.00)	3 (60.00)
P1 values		0.985			0.625		0.796
Combination therapy group (n=230)							
ACEIs/ARBs + Diuretics(n=12)	1 (8.33)	9 (75.00)	2 (16.67)	10 (83.33)	2 (16.67)	6 (50.00)	6 (50.00)
CCBs + Diuretics (n=9)	2 (22.22)	6 (66.67)	1 (11.11)	6 (66.67)	3 (33.33)	4 (44.44)	5 (55.56)
β-Bs + Diuretics (n=21)	1 (4.76)	18 (85.71)	2 (9.52)	15 (71.43)	6 (28.57)	6 (28.57)	15 (71.43)
ACEIs/ARBs + CCBs (n=36)	3 (8.33)	31 (86.11)	2 (5.56)	31 (86.11)	5 (13.89)	12 (33.33)	24 (66.67)
CCBs + β-Bs (n=69)	14 (20.29)	48 (69.57)	7 (10.14)	59 (85.51)	10 (14.49)	24 (34.78)	45 (65.22)
ACEI/ARB + β-B (n=26)	4 (15.38)	20 (76.92)	2 (7.69)	18 (69.23)	8 (30.77)	8 (30.77)	18 (69.23)
ACEIs/ARBs + β-Bs + CCBs (n=57)	10 (17.54)	41 (71.93)	6 (10.53)	51 (89.47)	6 (10.53)	21 (36.84)	36 (63.16)
P2 values		0.791			0.136		0.893
P3 values		0.968			0.299		0.969

Note: P1 represents the comparison results among groups within the monotherapy group, P2 represents the comparison results among groups within the combination therapy group, and P3 represents the comparison results among all groups. Fisher's exact test was used for comparisons among groups within the monotherapy group, among groups within the combination therapy group, and among all groups. ACEIs: angiotensin-converting enzyme inhibitors, ARBs: angiotensin receptor blockers, CCBs: calcium channel blockers, β-Bs: β-blockers.

Comparison of sitting DBP and SBP among antihypertensive drug groups

At baseline, sitting DBP and SBP did not differ significantly among the various antihypertensive drug groups (all P>0.05). After 8 weeks of treatment, both DBP and SBP decreased significantly in all groups, with a greater reduction observed in the combination therapy group compared with the monotherapy group (P<0.05). However, within-group comparisons among different antihypertensive regimens revealed no significant differences in blood pressure levels or reduction magnitude (P>0.05; **Table 3**).

Comparison of effective rates after 8 weeks of treatment

After 8 weeks, the effective rate of blood pressure control was significantly higher in the combination therapy group than in the monotherapy group (75.65% vs. 47.14%, P<0.05). Within the monotherapy group, the CCBs subgroup had a higher effective rate than other single-drug groups, though the difference was not statistically significant (P>0.05). Within the combination therapy group, the ACEIs/ARBs + CCBs and ACEIs/ARBs + β-Bs + CCBs regimens achieved higher effective rates than other combinations, but the differences were also not statistically significant (P>0.05; **Table 4**).

Comparison of anxiety and depression scores among different antihypertensive drug groups

At baseline, GAD-7 and PHQ-9 scores did not differ significantly among the various drug groups (both P>0.05). After 8 weeks, no significant difference in these scores was found between the monotherapy and combination therapy groups (P>0.05; **Table 5**).

In the monotherapy group, post-treatment GAD-7 and PHQ-9 scores significantly decreased in the ACEIs/ARBs group, while only PHQ-9 scores decreased significantly in the CCBs group (P<0.05). The post-treatment GAD-7 score in the ACEIs/ARBs group was significantly lower than that in the β-Bs group (P<0.05). For PHQ-9, scores in the ACEIs/ARBs group were significantly lower than those in both the CCB and β-B groups, and the CCBs group scored lower than the β-Bs group (all P<0.05).

In the combination therapy group, post-treatment GAD-7 and PHQ-9 scores decreased significantly in the ACEIs/ARBs + diuretic and ACEIs/ARBs + CCBs groups (P<0.05), both being significantly lower than those in other

Table 3. Changes in DBP and SBP in sitting position among patients in different antihypertensive drug groups [$\bar{x}$±s, n (%)]

Drug regimen	DBP in sitting position (mmHg)			SBP in sitting position (mmHg)		
	Baseline	After 8 weeks of treatment	Change	Baseline	After 8 weeks of treatment	Change
Monotherapy group (n=70)	97.53±5.76	85.94±5.59*	-11.57±8.28	152.64±10.27	132.74±11.87*	-19.90±15.71
ACEIs/ARBs (n=10)	96.60±5.06	84.00±6.09*	-12.60±8.34	154.70±14.41	136.60±13.91*	-18.10±20.65
CCBs (n=33)	97.09±6.18	85.76±5.38*	-11.33±8.75	153.21±10.15	131.03±12.68*	-22.18±16.24
β-Bs (n=22)	97.73±5.38	86.82±4.99*	-10.91±6.35	153.05±7.71	134.68±9.95*	-18.36±12.47
Diuretics (n=5)	101.40±5.90	87.20±8.78*	-14.20±13.70	143.00±9.38	127.80±8.64*	-15.20±16.69
F values	0.908	0.669	0.267	1.696	1.070	0.484
T values	0.442	0.574	0.849	0.176	0.368	0.695
Combination therapy group (n=230)	96.58±4.67	80.94±7.30*,a	-15.64±9.10*,a	150.47±9.67*,a	124.57±8.72*,a	-25.91±12.22*,a
ACEIs/ARBs + Diuretics (n=12)	95.50±3.40	80.17±8.70*	-15.33±10.00	151.00±11.29	126.42±8.33*	-24.58±10.82
CCBs + Diuretics (n=9)	94.67±5.07	83.00±7.04*	-11.67±7.37	150.56±10.20	123.44±8.82*	-27.11±10.74
β-Bs + Diuretics (n=21)	98.33±4.77	81.00±7.28*	-17.33±10.41	151.43±8.32	125.62±10.22*	-25.81±12.97
ACEIs/ARBs + CCBs (n=36)	96.03±4.42	80.94±5.94*	-15.08±7.33	150.61±8.55	125.86±10.47*	-24.75±13.26
CCBs + β-Bs (n=69)	96.99±4.81	81.73±7.91*	-15.26±9.89	150.26±8.55	124.41±9.27*	-25.86±11.74
ACEIs/ARBs + β-Bs (n=26)	96.42±5.49	80.62±7.69*	-15.81±10.01	152.04±7.78	126.46±8.87*	-25.58±12.49
ACEIs/ARBs + β-Bs + CCBs (n=57)	96.40±4.36	79.97±7.07*	-16.44±8.43	149.46±12.39	122.47±9.06*	-26.98±12.71
F values	1.042	0.447	0.519	0.261	0.906	0.165
t values	0.399	0.847	0.793	0.955	0.491	0.986

Note: Compared with baseline, *P<0.05; Compared with monotherapy, aP<0.05; SBP: systolic blood pressure, SDP: diastolic blood pressure, ACEIs: angiotensin-converting enzyme inhibitors, ARBs: angiotensin receptor blockers, CCBs: calcium channel blockers, β-Bs: β-blockers.

Table 4. Comparison of effective rates between different antihypertensive drug groups after 8 weeks of treatment [n (%)]

Project	Group	Number of cases	Number of effective persons	Effective rate
Analysis of differences within the Monotherapy group	ACEIs/ARBs	10	5	50.00%
	CCBs	33	18	54.55%
	β-Bs	22	8	36.36%
	Diuretics	5	2	40.00%
	X^2 values			1.887
	P values			0.596
Analysis of differences within the Combination therapy group	ACEIs/ARBs + Diuretics	12	9	75.00%
	CCBs + Diuretics	9	6	66.67%
	β-Bs + Diuretics	21	15	71.43%
	ACEIs/ARBs + CCBs	36	30	83.33%
	CCBs + β-Bs	69	49	71.01%
	ACEIs/ARBs + β-Bs	26	17	65.38%
	ACEIs/ARBs + β-Bs + CCBs	57	48	84.21%
	X^2 values			6.314
	P values			0.389
Overall effectiveness analysis	Combination therapy group	230	174	75.65%
	Monotherapy group	70	33	47.14%
	X^2 values			20.392
	P values			<0.001

Note: ACEIs: angiotensin-converting enzyme inhibitors, ARBs: angiotensin receptor blockers, CCBs: calcium channel blockers, β-Bs: β-blockers.

combination regimens (P<0.05). Among these, the ACEIs/ARBs + CCBs group showed the lowest scores (P<0.05). In contrast, patients in the β-B + diuretic group had significantly higher

Table 5. Comparison of anxiety and depression scores among different antihypertensive drug groups ($\bar{x}\pm s$)

Drug regimens	GAD-7 score		PHQ-9 score	
	Baseline	After 8 weeks of treatment	Baseline	After 8 weeks of treatment
Monotherapy group (n=70)	6.41±2.04	6.13±1.80	6.99±2.69	6.06±2.80
ACEIs/ARBs (n=10)	7.70±2.21	4.80±1.14*	6.50±3.06	3.60±1.51*
CCBs (n=33)	6.46±2.09	6.03±1.76	7.46±2.77	5.48±2.06*,a
β-Bs (n=22)	6.14±1.98	6.91±1.82a	6.86±2.42	8.23±3.01a,b
Diuretics (n=5)	6.20±1.92	6.00±1.73	5.40±2.41	5.20±1.79c
F values	0.423	3.597	1.039	10.927
P values	0.737	0.018	0.381	<0.001
Combination therapy group (n=230)	6.69±2.00	5.65±1.90	7.25±2.59	5.50±2.71
ACEIs/ARBs + Diuretics (n=12)	6.92±1.88	4.67±1.23*	7.00±2.22	4.17±2.08*
CCBs + Diuretics (n=9)	6.89±2.26	6.11±1.90a	7.67±2.78	6.44±2.24a
β-Bs + Diuretics (n=21)	7.00±1.97	7.67±2.22a,b	7.48±3.42	8.48±3.22a,b
ACEIs/ARBs + CCBs (n=36)	6.64±1.62	3.58±1.05*,a,b,c	7.47±2.13	2.44±1.65*,a,b,c
CCBs + β-Bs (n=69)	6.75±2.19	6.03±1.58a,c,d	7.04±2.42	6.29±2.05a,c,d
ACEIs/ARBs + β-Bs (n=26)	6.65±1.90	5.85±1.87a,c,d	8.00±2.87	6.27±2.44a,c,d
ACEIs/ARBs + β-Bs + CCBs (n=57)	6.47±2.10	5.79±1.46a,c,d	6.91±2.65	5.18±2.09c,d,e,f
F values	0.247	17.575	0.721	21.402
P values	0.960	<0.001	0.633	<0.001
Comparison between the Monotherapy group and the Combination therapy group				
t values	1.009	1.878	0.735	1.499
P values	0.314	0.061	0.463	0.135

Note: (1) Within the monotherapy group: Compared with the baseline, *P<0.05; Compared with the ACEIs/ARBs group, aP<0.05; Compared with the CCBs group, bP<0.05; Compared with the β-Bs group, cP<0.05. (2) Within the combined medication treatment group: Compared with the baseline, *P<0.05; Compared with the ACEIs/ARBs + diuretic group, aP<0.05; Compared with the CCBs + diuretic group, bP<0.05; Compared with the β-Bs + diuretic group, cP<0.05; Compared with the ACEIs/ARBs + CCBs group, dP<0.05; Compared with the CCBs + β-Bs group, eP<0.05; Compared with the ACEIs/ARBs + β-Bs group, fP<0.05. (3) ACEIs: angiotensin-converting enzyme inhibitors, ARBs: angiotensin receptor blockers, CCBs: calcium channel blockers, β-Bs: β-blockers.

GAD-7 and PHQ-9 scores after treatment compared with all other combinations (P<0.05; **Table 5**).

Comparison of sleep quality scores among antihypertensive drug groups

At baseline, no significant differences were observed in PSQI scores among the antihypertensive drug groups (P>0.05). After 8 weeks, PSQI scores did not differ significantly between the monotherapy and combination therapy groups (P>0.05; **Table 6**). In the monotherapy group, only the ACEIs/ARBs subgroup showed a significant reduction in PSQI score after treatment, which was also significantly lower than that of other single-drug groups (P<0.05).

In the combination therapy group, only the ACEIs/ARBs + CCBs subgroup showed a significant reduction in PSQI score compared with baseline, which was also significantly lower than those of other combinations (P<0.05). Conversely, PSQI scores increased significantly in the β-Bs + diuretic group and were higher than in other combination regimens (P<0.05; **Table 6**).

Comparison of safety evaluation among different antihypertensive drug groups

There were no significant differences in the incidence or severity (grades 1-3) of drug-related adverse reactions among the groups (P>0.05; **Table 7**).

Analysis of influencing factors of poor efficacy

Univariate analysis of poor efficacy: After 8 weeks of treatment, 93 patients (31.0%) exhibited poor efficacy, while 207 patients (69.0%) showed good efficacy. Compared with the good efficacy group, patients with poor efficacy had higher proportions of coronary heart disease, lower educational level (junior high school or below), moderate-to-severe carotid artery stenosis, carotid plaques, and monotherapy use, as well as higher PIV and SII values and larger carotid plaque area (all P<0.05; **Table 8**).

Table 6. Comparison of sleep quality scores among patients in different antihypertensive drug groups ($\bar{x}\pm s$)

Drug regimens	PSQI score	
	Baseline	After 8 weeks of treatment
Monotherapy group (n=70)	8.37±2.72	7.84±2.95
ACEIs/ARBs (n=10)	8.90±2.92	4.70±2.87*
CCBs (n=33)	8.49±2.40	7.67±2.34[a]
β-Bs (n=22)	8.09±2.89	9.59±2.72[a,b]
Diuretics (n=5)	7.80±4.15	7.60±2.61[a]
F values	0.286	8.522
P values	0.835	<0.001
Combination therapy group (n=230)	8.43±2.29	7.43±2.81
ACEIs/ARBs + Diuretics (n=12)	8.00±3.19	6.42±2.64
CCBs + Diuretics (n=9)	8.33±2.65	7.22±2.39
β-Bs + Diuretics (n=21)	8.48±2.21	9.90±2.59[a,b,*]
ACEIs/ARBs + CCBs (n=36)	8.56±2.06	3.83±2.12[a,b,c,*]
CCBs + β-Bs (n=69)	8.68±2.05	7.99±2.09[a,c,d]
ACEIs/ARBs + β-Bs (n=26)	8.92±2.42	8.15±2.33[a,c,d]
ACEIs/ARBs + β-Bs + CCBs (n=57)	7.91±2.41	8.02±2.33[a,c,d]
F values	0.916	21.371
P values	0.484	<0.001
Comparison between the Monotherapy group and the Combination therapy group		
t values	0.164	1.073
P values	0.870	0.284

Note: (1) Within the Monotherapy group: Compared with the baseline, *P<0.05; Compared with the ACEIs/ARBs group, [a]P<0.05; Compared with the CCBs group, [b]P<0.05. (2) Within the Combination therapy group: Compared with the baseline, *P<0.05; Compared with the ACEIs/ARBs + diuretic group, [a]P<0.05; Compared with the CCBs + diuretic group, [b]P<0.05; Compared with the β-Bs + diuretic group, [c]P<0.05; Compared with the ACEIs/ARBs + CCBs group, [d]P<0.05. (3) PSQI: Pittsburgh Sleep Quality Index, ACEIs: angiotensin-converting enzyme inhibitors, ARBs: angiotensin receptor blockers, CCBs: calcium channel blockers, β-Bs: β-blockers.

Multivariate logistic regression analysis of poor efficacy: Using efficacy (good = 0, poor = 1) as the dependent variable, variables with statistical significance in the univariate analysis were entered into a multivariate logistic regression model. Variable assignments were as follows: coronary heart disease (no = 0, yes = 1); educational level (junior high school or below = 0, high school or above = 1); carotid artery stenosis (normal = 0, mild = 1, moderate-to-severe = 2); medication regimen (monotherapy = 0, combination = 1); PIV, SII, and carotid plaque area were treated as continuous variables.

The results showed that coronary heart disease, high PIV values, moderate-to-severe carotid artery stenosis, and larger carotid plaque area were significantly associated with an increased risk of poor efficacy (P<0.05). Conversely, combination therapy and higher educational level (high school or above) were protective factors against poor efficacy (P<0.05; **Figure 1**).

Discussion

Effective management of hypertension depends fundamentally on achieving sustained blood pressure control. Poorly controlled blood pressure leads to progressive vascular and organ damage, thereby increasing morbidity and mortality from cardiovascular and renal complications [16]. Selecting an optimal therapeutic regimen that provides both effective and stable blood pressure reduction remains a major goal in clinical practice, particularly in the elderly population, who often present with multiple comorbidities and complex pathophysiological changes. In the present study, combination therapy produced a greater reduction in

Table 7. Safety evaluation of different antihypertensive drug groups [n (%)]

Drug regimens	Adverse events	Level 1	Level 2	Level 3	Drug-related adverse reactions
Monotherapy group (n=70)	29 (41.43)	24 (34.29)	3 (4.29)	2 (2.86)	9 (12.86)
ACEIs/ARBs (n=10)	4 (40.00)	4 (40.00)	0 (0.00)	0 (0.00)	1 (10.00)
CCBs (n=33)	13 (39.39)	10 (30.30)	2 (6.06)	1 (3.03)	4 (12.12)
β-Bs (n=22)	10 (45.45)	8 (36.36)	1 (4.55)	1 (4.55)	3 (13.64)
Diuretics (n=5)	2 (40.00)	2 (40.00)	0 (0.00)	0 (0.00)	1 (20.00)
P values	0.975	0.921	0.818	0.880	0.853
Combination therapy group (n=230)	83 (36.09)	70 (30.43)	10 (4.35)	3 (1.30)	40 (17.39)
ACEIs/ARBs + Diuretics (n=12)	4 (33.33)	4 (33.33)	0 (0.00)	0 (0.00)	2 (16.67)
CCBs + Diuretics (n=9)	3 (33.33)	3 (33.33)	0 (0.00)	0 (0.00)	2 (22.22)
β-Bs + Diuretics (n=21)	9 (42.86)	8 (38.10)	1 (4.76)	0 (0.00)	4 (19.05)
ACEIs/ARBs + CCBs (n=36)	12 (33.33)	11 (30.56)	1 (2.78)	0 (0.00)	5 (13.89)
CCBs + β-Bs (n=69)	25 (36.23)	21 (30.43)	3 (4.35)	1 (1.45)	13 (18.84)
ACEIs/ARBs + β-Bs (n=26)	9 (34.62)	8 (30.77)	1 (3.85)	0 (0.00)	4 (15.38)
ACEIs/ARBs + β-Bs + CCBs (n=57)	21 (36.84)	15 (26.32)	4 (7.02)	2 (3.51)	10 (17.54)
P values	0.996	0.980	0.903	0.739	0.995
Comparison between the Monotherapy group and the Combination therapy group					
X^2 values	1.100	0.370	-	-	-
P values	0.294	0.543	0.641	0.332	0.241

Note: ACEIs: angiotensin-converting enzyme inhibitors, ARBs: angiotensin receptor blockers, CCBs: calcium channel blockers, β-Bs: β-blockers.

both systolic and diastolic blood pressure than monotherapy (P<0.05). The overall effective rate of the combination therapy group (75.65%) was higher than that of the monotherapy group (47.14%) (P<0.05), while no significant differences were observed among specific combination regimens. These findings suggest that combining antihypertensive agents yields superior control in elderly hypertensive patients, and that the overall therapeutic benefit depends more on the use of multiple mechanisms rather than the specific drug combination itself. Moreover, multivariate analysis indicated that combination therapy independently reduced the risk of poor blood pressure control, even after adjusting for potential confounders, further reinforcing its clinical advantage.

These results are consistent with previous research showing that over two-thirds of hypertensive patients fail to achieve target control using monotherapy [17]. Large-scale studies have demonstrated that multidrug regimens are more effective in achieving blood pressure goals and reducing cardiovascular risk than single-agent therapy [18-20]. Combination therapy optimizes antihypertensive efficacy by targeting multiple physiological pathways simultaneously, thereby enhancing the complementary pharmacological actions of different agents [21]. In this study, the ACEIs/ARBs + CCBs dual regimen exhibited a higher effective rate than ACEIs/ARBs or CCBs monotherapy, consistent with the findings of Hong et al. [20], although this difference did not reach statistical significance. The observed trend likely reflects the synergistic effects of these drug classes. Mechanistically, ACEIs or ARBs and CCBs jointly lower intracellular calcium concentrations and inhibit the reflex activation of the renin-angiotensin system induced by calcium channel blockade, leading to enhanced vasodilation and more sustained blood pressure reduction [22, 23]. Importantly, combination therapy did not increase adverse drug reactions. The incidence and severity of drug-related adverse events (grades 1-3) did not differ significantly among groups, consistent with earlier findings indicating that multidrug regimens do not compromise safety [20].

Accumulating evidence has revealed a bidirectional association between hypertension and psychiatric disorders such as depression, anxiety, and sleep disturbances [24]. Chronic hypertension can affect cerebral perfusion and neurochemical homeostasis, contributing to mood and sleep disorders, while psychological stress and sleep impairment may, in turn, exacerbate sympathetic activation and blood pres-

Table 8. Univariate analysis of poor efficacy [$\bar{x}\pm s$, M (P25, P75), n (%)]

Information	Poor efficacy group (n=93)	Good efficacy group (n=207)	t/z/x^2 values	*P* values
Gender			1.561	0.211
Male	49 (52.69)	125 (60.39)		
Female	44 (47.31)	82 (39.61)		
Age	73.51±5.33	73.44±5.17	0.101	0.920
BMI (kg/m^2)	26.31±3.07	25.92±2.65	1.121	0.263
Place of residence			2.089	0.148
Rural area	40 (43.01)	71 (34.30)		
City	53 (56.99)	136 (65.70)		
Course of disease	13.00 (8.00, 16.00)	11.00 (6.00, 15.00)	1.923	0.054
History of smoking	20 (21.51)	42 (20.29)	0.058	0.810
History of alcohol consumption	16 (17.20)	36 (17.39)	0.002	0.968
Diabetes mellitus	20 (21.51)	41 (19.81)	0.114	0.735
Coronary heart disease	40 (43.01)	64 (30.92)	4.143	0.042
Complicated chronic kidney disease	16 (17.20)	24 (11.59)	1.748	0.186
Combined with hyperlipidemia	20 (21.51)	35 (16.91)	0.906	0.341
Educational level			5.999	0.014
Junior high school and below	56 (60.22)	93 (44.93)		
High school and above	37 (39.78)	114 (55.07)		
PIV	220.80 (162.74, 346.07)	191.20 (151.87, 229.81)	3.398	0.001
SII	583.04 (442.11, 786.44)	434.83 (362.65, 549.51)	4.977	<0.001
Baseline SBP (mmHg)	151.18±10.17	150.89±9.71	0.239	0.811
Baseline SDP (mmHg)	96.51±5.61	96.94±4.64	0.698	0.486
Baseline GAD-7 score	6.54±1.97	6.67±2.03	0.513	0.608
Baseline PHQ-9 score	6.99±2.85	7.28±2.50	0.877	0.381
Baseline PSQI score	8.37±2.57	8.44±2.32	0.247	0.805
Degree of carotid artery stenosis			16.525	<0.001
Normal	55 (59.14)	154 (74.40)		
Mild stenosis	15 (16.13)	37 (17.87)		
Moderate to severe stenosis	23 (24.73)	16 (7.73)		
Carotid plaques were present	44 (47.31)	72 (34.78)	4.248	0.039
Carotid plaque area (mm^2)	0.00 (0.00, 33.43)	0.00 (0.00, 24.39)	2.586	0.010
Drug regimens			20.392	<0.001
Monotherapy	37 (39.78)	33 (15.94)		
Drug combinations	56 (60.22)	174 (84.06)		

Notes: BMI: body mass index, PIV: pan-immune inflammation index, SII: systemic immune inflammation index, SBP: systolic blood pressure, SDP: diastolic blood pressure, GAD-7: Generalized anxiety disorder scale, PHQ-9: Patient Health Questionnaire-9, PSQI: Pittsburgh Sleep Quality Index scale.

sure elevation. Hence, clinical management of hypertension should encompass not only hemodynamic control but also attention to patients' psychological well-being. In the current study, ACEIs/ARBs monotherapy and ACEIs/ARBs combined with CCBs significantly improved anxiety, depression, and sleep quality in elderly hypertensive patients, while CCBs monotherapy also alleviated depressive symptoms to some extent. These findings support the hypothesis that RAS blockade exerts beneficial neuropsychological effects beyond its antihypertensive properties.

A growing body of evidence indicates that ACEIs and ARBs have intrinsic anxiolytic and antidepressant potential. Animal studies have shown that ACEI agents such as captopril and lisinopril

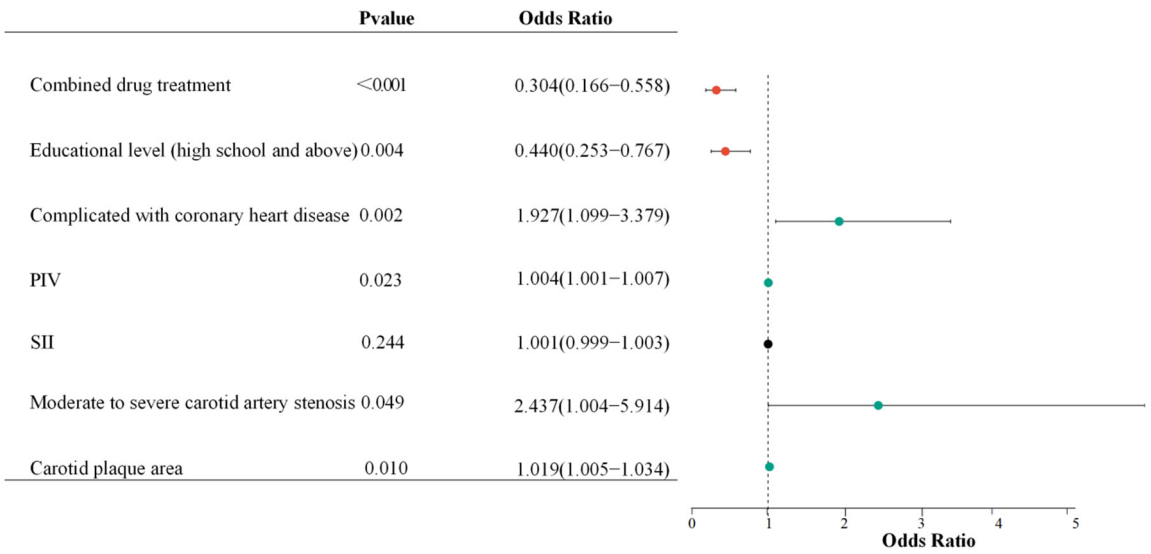

Figure 1. Multivariate logistic regression analysis of poor efficacy (Notes: PIV: pan-immune inflammation index, SII: systemic immune inflammation index).

mitigate stress-induced depression-like behaviors through modulation of the bradykinin/mammalian target of rapamycin complex 1 (mTORC1) pathway [25]. Clinical observations have further demonstrated that captopril and ARBs such as candesartan and losartan reduce anxiety and improve emotional stability [26, 27]. A meta-analysis encompassing 11 randomized controlled trials reported that ACEI/ARB therapy significantly improved mental health-related quality of life - specifically overall well-being, positive mood, and anxiety scores - compared with placebo or non-RAS inhibitors [28]. The neurobiological mechanisms underlying these effects are multifactorial. ACEIs and ARBs inhibit the binding of angiotensin II (Ang II) to AT1 receptors, thereby suppressing excessive hypothalamic-pituitary-adrenal (HPA) axis activation and attenuating stress responses. Ang II promotes proinflammatory cytokine release, such as IL-6, while certain ARBs (e.g., telmisartan) can cross the blood-brain barrier and directly ameliorate neuroinflammation [29, 30]. Moreover, by improving vascular endothelial function and stabilizing carotid plaques, ACEI/ARB therapy enhances cerebral blood flow to the hippocampus and prefrontal cortex, thereby alleviating vascular-related depressive and anxiety symptoms. In terms of sleep regulation, ARBs can reduce sympathetic excitability and prolong slow-wave (N3-stage) sleep duration, which contributes to better sleep quality [31].

The combination of ACEIs/ARBs with CCBs appeared to yield the greatest improvement in psychiatric symptoms. This may be attributed to the additive or synergistic neuroprotective and vascular effects of these agents. Preclinical evidence shows that several CCBs exhibit anxiolytic-like effects. Nimodipine, for example, reduces fear conditioning in mice by limiting neurotransmitter release and excitatory postsynaptic currents in the amygdala [32], whereas diltiazem enhances neurosteroid production in the brain, resulting in anxiolytic-like behavior [33]. However, findings from human studies regarding the relationship between CCBs use and depression remain inconsistent. Some cohort analyses suggest that CCBs therapy reduces depression risk [34], whereas others associate CCBs use with increased hospitalization for mood disorders [35]. These discrepancies may stem from heterogeneity in patient populations, outcome definitions, and confounder control. The neuropsychological influence of CCBs is likely mediated through their effects on L-type calcium channels (Cav1.2 and Cav1.3) in the brain. By modulating glutamate and GABA neurotransmission and synaptic plasticity, CCBs can influence activity within emotion-regulating regions such as the prefrontal cortex and hippocampus [36]. In addition, they regulate neuroinflammation through NF-κB-related signaling, reduce microglial overactivation, promote neurosteroid synthesis,

and lower oxidative stress. These pathways may act synergistically with ACEIs/ARBs to alleviate anxiety and depressive symptoms [37].

In contrast, β-blockers monotherapy and β-blockers combined with diuretics were found to exacerbate depressive symptoms and sleep disturbances. Prior reviews have highlighted that β-blockers, particularly lipophilic agents such as propranolol, can cross the blood-brain barrier and interfere with central noradrenergic signaling, leading to fatigue, lethargy, and depressed mood. These neurochemical changes disrupt emotional regulation and may provoke depression-like symptoms. Additionally, diuretics can induce electrolyte imbalances - particularly hypokalemia and hyponatremia - which may provoke neurological manifestations including mood fluctuations and sleep rhythm disturbances. Such electrolyte changes may also alter the pharmacodynamics of psychotropic medications, either diminishing efficacy or exacerbating side effects [38]. The concomitant use of β-blockers and diuretics may therefore amplify these neuropsychiatric effects through overlapping physiological pathways, consistent with the present observations.

Despite significant therapeutic advances, the overall rate of blood pressure target attainment in elderly hypertensive patients remains suboptimal. In this study, the control rate was 69.00%, similar to that reported by Lee HY et al. (65.56%) in an elderly cohort [39]. Both studies indicate that over 30% of patients fail to achieve optimal control, underscoring the need to identify determinants of therapeutic resistance. The current analysis revealed that comorbid coronary heart disease, elevated PIV values, moderate-to-severe carotid stenosis, and larger carotid plaque areas were independently associated with poor treatment efficacy, whereas combination therapy and higher educational level (senior high school or above) were protective factors. PIV, as an integrated marker of systemic immune-inflammatory activation, reflects heightened inflammatory status [40]. In hypertensive individuals, persistent high blood pressure causes endothelial injury, while increased PIV may accelerate carotid intimal thickening, lipid deposition, and plaque progression by enhancing proinflammatory cytokine secretion (e.g., TNF-α, IL-6) and oxidative stress [41]. These vascular inflammatory processes can impair local perfusion and may also blunt responsiveness to antihypertensive therapy via systemic inflammatory signaling, representing a potential biological mechanism underlying reduced treatment efficacy.

Patients with concomitant coronary heart disease often exhibit more extensive vascular pathology and structural or functional cardiac abnormalities, including myocardial hypertrophy and reduced cardiac reserve capacity. Such comorbidities complicate hemodynamic regulation and increase the difficulty of blood pressure control, thereby diminishing the effectiveness of antihypertensive therapy [42]. Collectively, these findings emphasize that vascular inflammation, endothelial dysfunction, and comorbid atherosclerotic disease contribute significantly to therapeutic resistance in elderly hypertensive patients, suggesting that comprehensive management strategies should incorporate anti-inflammatory and vascular-protective interventions.

This study has several limitations. First, as a single-center study with a relatively limited sample size, the possibility of selection bias cannot be excluded. Second, because of its retrospective design, certain variables that might influence therapeutic response were unavailable, restricting the inclusion of potentially relevant confounding factors. Future multicenter, prospective studies with larger cohorts and longer follow-up periods are warranted to validate these findings and explore the longitudinal relationship between inflammatory markers, vascular remodeling, psychiatric symptoms, and antihypertensive outcomes.

In conclusion, combination therapy provides superior antihypertensive efficacy compared with monotherapy in elderly patients, without increasing the incidence of adverse events or drug-related reactions. Among the various regimens, ACEIs/ARBs monotherapy and particularly ACEIs/ARBs combined with CCBs demonstrated the most favorable effects on both blood pressure control and psychiatric symptoms, whereas β-blockers, especially when combined with diuretics, may negatively affect mood and sleep. When selecting antihypertensive strategies for elderly patients, clinicians should consider not only hemodynamic efficacy but also psychological comorbidities, vascular

inflammatory status, carotid pathology, and educational background. ACEIs/ARBs-based combination therapy - particularly ACEIs/ARBs + CCBs - should be prioritized to achieve optimal blood pressure.

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Disclosure of conflict of interest

None.

Address correspondence to: Miao Lu, Department of Geriatrics Medicine, Jiangsu Province Hospital (The First Affiliated Hospital with Nanjing Medical University), No. 300, Guangzhou Road, Nanjing 210029, Jiangsu, China. Tel: +86-13952031659; E-mail: lumiao@jsph.org.cn

References

[1] Fuchs FD and Whelton PK. High blood pressure and cardiovascular disease. Hypertension 2020; 75: 285-292.

[2] Korosi B, Laszlo A, Tabak A, Batta D, Lenart L, Fekete A, Eorsi D, Cseprekal O, Tisler A, Nemcsik-Bencze Z, Gonda X, Rihmer Z and Nemcsik J. The impact of currently recommended antihypertensive therapy on depression and other psychometric parameters: preliminary communication. Neuropsychopharmacol Hung 2017; 19: 11-22.

[3] Graham N and Smith DJ. Comorbidity of depression and anxiety disorders in patients with hypertension. J Hypertens 2016; 34: 397-8.

[4] Figueiredo CA, Nunes DP, Fusco SB and Saidel MGB. Mental health of elderly hypertensive patients in primary health care: an integrative review. Aquichan 2023; 23: e2347.

[5] Yao YJ, Gui M and Cai SK. A network meta-analysis comparative the efficacy of angiotensin-converting enzyme inhibitors and calcium channel blockers in hypertension. Medicine (Baltimore) 2024; 103: e37856.

[6] Kichou B, Bouraghda A, Lahmar HMA, Amara S, Aoudia Y, Benchabi Y, Haddoum F, Kachenoura A, Laredj N, Manamani L, Bouafia MTC and Chettibi M. The role of single-pill ACE inhibitor/ccb combination for hypertension: an Algerian view via the nominal group technique. Future Cardiol 2025; 21: 155-166.

[7] Wang JG, Topouchian J, Bricout-Hennel S, Mu J, Chen L, Li P, He S, Luo S, Jiang W, Jiang Y, Sun Y, Zhang Y and Asmar R. Efficacy and safety of a single-pill versus free combination of perindopril/indapamide/amlodipine: a multicenter, randomized, double-blind study in Chinese patients with hypertension. J Hypertens 2024; 42: 1373-1381.

[8] Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V and Desormais I; ESC Scientific Document Group. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J 2018; 39: 3021-3104.

[9] Aslan I, Ochnik D and Çınar O. Exploring perceived stress among students in turkey during the COVID-19 pandemic. Int J Environ Res Public Health 2020; 17: 8961.

[10] Kroenke K, Spitzer RL and Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001; 16: 606-13.

[11] Oliveira-Silva L, Peçanha T, Fecchio RY, Rezende RA, Abreu A, Silva G, Mion-Junior D, Cipolla-Neto J, Forjaz CLM and Brito LC. Poor sleep quality is associated with cardiac autonomic dysfunction in treated hypertensive men. J Clin Hypertens (Greenwich) 2020; 22: 1484-1490.

[12] Naylor AR, Rothwell PM and Bell PR. Overview of the principal results and secondary analyses from the European and North American randomised trials of endarterectomy for symptomatic carotid stenosis. Eur J Vasc Endovasc Surg 2003; 26: 115-29.

[13] Jiang B, He D, Zhang L and Ye M. Risk prediction of cerebrovascular events with carotid plaque magneitc resonance analysis: a meta-analysis. J Neuroradiol 2019; 46: 117-123.

[14] Ferguson GG, Eliasziw M, Barr HW, Clagett GP, Barnes RW, Wallace MC, Taylor DW, Haynes RB, Finan JW, Hachinski VC and Barnett HJ. The North American Symptomatic Carotid Endarterectomy Trial: surgical results in 1415 patients. Stroke 1999; 30: 1751-8.

[15] Chen AP, Setser A, Anadkat MJ, Cotliar J, Olsen EA, Garden BC and Lacouture ME. Grading dermatologic adverse events of cancer treatments: the Common Terminology Criteria for Adverse Events Version 4.0. J Am Acad Dermatol 2012; 67: 1025-39.

[16] Zhou B, Perel P, Mensah GA and Ezzati M. Global epidemiology, health burden and effec-

tive interventions for elevated blood pressure and hypertension. Nat Rev Cardiol 2021; 18: 785-802.
[17] Tocci G, Presta V, Citoni B, Figliuzzi I, Bianchi F, Ferrucci A and Volpe M. Blood pressure target achievement under monotheraphy: a real-life appraisal. High Blood Press Cardiovasc Prev 2020; 27: 587-596.
[18] Ogawa H, Kim-Mitsuyama S, Matsui K, Jinnouchi T, Jinnouchi H and Arakawa K; OlmeSartan and Calcium Antagonists Randomized (OSCAR) Study Group. Angiotensin II receptor blocker-based therapy in Japanese elderly, high-risk, hypertensive patients. Am J Med 2012; 125: 981-90.
[19] Hu D, Liu L and Li W. Efficacy and safety of valsartan/amlodipine single-pill combination in 11,422 Chinese patients with hypertension: an observational study. Adv Ther 2014; 31: 762-75.
[20] Hong SJ, Jeong HS, Han SH, Chang KY, Hong BK, Lee BK, Chae SC, Kim WS, Park CG, Heo JH, Lee SU, Kim YD, Kim KS, Choi JH, Kang HJ, Kim JJ, Kang SM, Choi YJ, Shin JH, Chun KJ, Shin DG, Park SH, Kwan J, Choi YJ, Jeong MH, Chae JK, Kim DW, Cho JR, Han KR, Won KH, Park SH, Lee SK, Kim SH, Jung J and Kim CH. Comparison of fixed-dose combinations of Amlodipine/Losartan Potassium/Chlorthalidone and Amlodipine/Losartan Potassium in patients with stage 2 hypertension inadequately controlled with Amlodipine/Losartan Potassium: a randomized, double-blind, multicenter, phase III study. Clin Ther 2017; 39: 2049-2060.
[21] Marinier K, Macouillard P, de Champvallins M, Deltour N, Poulter N and Mancia G. Effectiveness of two-drug therapy versus monotherapy as initial regimen in hypertension: a propensity score-matched cohort study in the UK Clinical Practice Research Datalink. Pharmacoepidemiol Drug Saf 2019; 28: 1572-1582.
[22] Brewster LM, Boermeester AS, Seedat YK and Van Montfrans GA. Initial combination therapy for hypertension in patients of African ancestry: a systematic review and meta-analysis. J Hypertens 2022; 40: 629-640.
[23] Te Riet L, van Esch JH, Roks AJ, van den Meiracker AH and Danser AH. Hypertension: renin-angiotensin-aldosterone system alterations. Circ Res 2015; 116: 960-75.
[24] Qin J, He Z, Wu L, Wang W, Lin Q, Lin Y and Zheng L. Prevalence of mild cognitive impairment in patients with hypertension: a systematic review and meta-analysis. Hypertens Res 2021; 44: 1251-1260.
[25] Luo H, Wu PF, Cao Y, Jin M, Shen TT, Wang J, Huang JG, Han QQ, He JG, Deng SL, Ni L, Hu ZL, Long LH, Wang F and Chen JG. Angiotensin-converting enzyme inhibitor rapidly ameliorates depressive-type behaviors via bradykinin-dependent activation of mammalian target of rapamycin complex 1. Biol Psychiatry 2020; 88: 415-425.
[26] Saavedra JM, Armando I, Bregonzio C, Juorio A, Macova M, Pavel J and Sanchez-Lemus E. A centrally acting, anxiolytic angiotensin II AT1 receptor antagonist prevents the isolation stress-induced decrease in cortical CRF1 receptor and benzodiazepine binding. Neuropsychopharmacology 2006; 31: 1123-34.
[27] Srinivasan J, Suresh B and Ramanathan M. Differential anxiolytic effect of enalapril and losartan in normotensive and renal hypertensive rats. Physiol Behav 2003; 78: 585-91.
[28] Brownstein DJ, Salagre E, Köhler C, Stubbs B, Vian J, Pereira C, Chavarria V, Karmakar C, Turner A, Quevedo J, Carvalho AF, Berk M and Fernandes BS. Blockade of the angiotensin system improves mental health domain of quality of life: a meta-analysis of randomized clinical trials. Aust N Z J Psychiatry 2018; 52: 24-38.
[29] Sizhu G and Fang D. Renin-angiotensin system: the underlying mechanisms and promising therapeutical target for depression and anxiety. Front Immunol 2023; 13: 1053136.
[30] Villapol S, Janatpour ZC, Affram KO and Symes AJ. The renin angiotensin system as a therapeutic target in traumatic brain injury. Neurotherapeutics 2023; 20: 1565-1591.
[31] Gong S and Deng F. Renin-angiotensin system: the underlying mechanisms and promising therapeutical target for depression and anxiety. Front Immunol 2023; 13: 1053136.
[32] Shinnick-Gallagher P, McKernan MG, Xie J and Zinebi F. L-type voltage-gated calcium channels are involved in the in vivo and in vitro expression of fear conditioning. Ann N Y Acad Sci 2003; 985: 135-49.
[33] Yoshizawa K, Nakashima K, Tabuchi M, Okumura A, Nakatake Y, Yamada M, Tsuneoka Y and Higashi T. Benzothiazepines, diltiazem and JTV-519, exert an anxiolytic-like effect via neurosteroid biosynthesis in mice. J Pharmacol Sci 2020; 143: 234-237.
[34] Bojanić I, Bjerkeset O, Williams LJ, Berk M, Sund ER and Sletvold H. Associations of cardiovascular agents and metformin with depression symptoms: a cross-sectional analysis from the HUNT study, norway. Drugs Real World Outcomes 2022; 9: 503-516.
[35] Boal AH, Smith DJ, McCallum L, Muir S, Touyz RM, Dominiczak AF and Padmanabhan S. Monotherapy with major antihypertensive drug classes and risk of hospital admissions for mood disorders. Hypertension 2016; 68: 1132-1138.

[36] Kabir ZD, Martínez-Rivera A and Rajadhyaksha AM. From gene to behavior: L-type calcium channel mechanisms underlying neuropsychiatric symptoms. Neurotherapeutics 2017; 14: 588-613.

[37] Colbourne L and Harrison PJ. Brain-penetrant calcium channel blockers are associated with a reduced incidence of neuropsychiatric disorders. Mol Psychiatry 2022; 27: 3904-3912.

[38] Carnovale C, Perrotta C, Baldelli S, Cattaneo D, Montrasio C, Barbieri SS, Pompilio G, Vantaggiato C, Clementi E and Pozzi M. Antihypertensive drugs and brain function: mechanisms underlying therapeutically beneficial and harmful neuropsychiatric effects. Cardiovasc Res 2023; 119: 647-667.

[39] Lee HY, Min KW, Han KA, Kim JS, Ahn JC, Kim MH, Lee JB, Shin SH, Kim CJ, Kim KH, Cho DK, Choi J, Rhee MY, Her SH, Kim W, Na JO, Cho GY, Kim SY, Park GM, Lee BK, Jo SH, Lee BW, Sohn IS, Kim DI, Ihm SH, Lee SH, Chung JW, Cho EJ, Son JW, Oh SJ, Hwang JY, Jeong JO, Han KR, Yoon HJ, Seo SM, Chung WJ, Bae JW, Choi JH, Hyun BJ, Cha JE, Yoo SJ and Shin J. The efficacy and tolerability of Irbesartan/Amlodipine combination therapy in patients with essential hypertension whose blood pressure were not controlled by irbesartan monotherapy. Clin Ther 2024; 46: 481-489.

[40] Karacan Gölen M, Uçar Karabulut K, Kamiloğlu M and Yonar A. Pan-immune-inflammation value predicts 3-month functional outcomes in patients with acute ischemic stroke treated with mechanical thrombectomy. Brain Behav 2025; 15: e70397.

[41] Li X, Guo D, Hu Y and Chen Y. Oxidative stress and inflammation are associated with coexistent severe multivessel coronary artery stenosis and right carotid artery severe stenosis in elderly patients. Oxid Med Cell Longev 2021; 2021: 2976447.

[42] Rosendorff C, Lackland DT, Allison M, Aronow WS, Black HR, Blumenthal RS, Cannon CP, de Lemos JA, Elliott WJ, Findeiss L, Gersh BJ, Gore JM, Levy D, Long JB, O'Connor CM, O'Gara PT, Ogedegbe G, Oparil S and White WB; American Heart Association, American College of Cardiology, and American Society of Hypertension. Treatment of hypertension in patients with coronary artery disease: a scientific statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension. Circulation 2015; 131: e435-70.