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Development and Validation of a Medication Selection Model Under Clinical Application of Renin-Angiotensin Inhibitor Combined with Calcium Channel Blocker for Hypertension Patients

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: This study evaluated the impact of clinical features and concomitant conditions on the clinical selection of different renin-angiotensin system (RAS) inhibitors in patients with hypertension, and built a renin-angiotensin inhibitors selection model (RAISM) to provide a reference for clinical decision making.

Material/Methods: We included 213 hypertensive patients in the study cohort; patients were divided into two groups: the angiotensin-converting enzyme inhibitor (ACEI) combined with calcium channel blocker (CCB) group (ACEI+CCB group) and the angiotensin receptor antagonist (ARB) combined with CCB group (ARB+CCB group). Basic demographic characteristics and concomitant conditions of the patients were compared. Single-factor and multi-factor analysis was performed by adopting logistic regression model. The RAISM was established by utilizing the nomograph technology. C-index and calibration curve were used to evaluate the model's efficacy.

Results: In the study, 34.27% of the patients used ACEI+CCB and 65.73% of patients used ARB+CCB. The difference in age, body mass index (BMI), elderly patient, diabetes, renal dysfunction, and hyperlipidemia between the 2 groups determined medication selection. To be specific, compared to the group using ARB+CCB, the odds ratios and 95% confidence interval (CI) of the aforementioned factors for the ACEI+CCB group were 0.476 (0.319–0.711), 1.274 (1.001–1.622), 0.365 (0.180–0.743), 0.471 (0.203–1.092), 0.542 (0.268–1.094), and 0.270 (0.100–0.728), respectively; The C-index of RAISM acquired from the model construction parameters was 0.699, and the correction curve demonstrated that the model has good discriminative ability.

Conclusions: The outcome of our study suggests that independent discriminating factors that influence the clinical selection of different RAS inhibitors were elderly patient, renal insufficiency, and hyperlipidemia; and the RAISM constructed in this study has good predictability and clinical benefit.

MeSH Keywords: Artificial Intelligence • Decision Support Systems, Clinical • Hypertension • Knowledge Management • Medication Therapy Management

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Background

Hypertension is the major cause of global cardiovascular diseases (CVDs) and CVD mortality, and the economic burden related to hypertension is as much as 370 billion dollars [1,2]. As the most populous country in the world, China's burden of hypertension is increasing accordingly [3]. In China, the prevalence of hypertension has been on the rise for the past 20 years and up to 27.9% of the adult population developed hypertension according to the latest national census data [4]. The disability-adjusted life years (DALY) as a result of hypertension in the Chinese population has reached 37.94 million, accounting for 12.0% of the total DALY and 63.5% of the CVDs-related DALY of CVDs [5,6]. About 50% of strokes and 40% of myocardial infarctions are related to hypertension [7,8]. With the aging of the population, the rapid development of urbanization, and changes in lifestyle and eating habits, the prevalence and burden of hypertension will continue to rise among the Chinese population.

Medication is the most effective intervention for blood pressure control. The over-activated renin-angiotensin system (RAS) is one of the major causes of hypertension [9]. In the latest European cardiovascular guideline [10], RAS inhibitors combined with calcium channel blocker (CCB) have been recommended as the primary choice for hypertension first-line medication. The Chinese Hypertension Intervention Efficacy (CHIEF) research report showed that when a small dose of amlodipine combined with RAS inhibitors was used for the first time, the blood pressure level of hypertension patients could be significantly reduced, and the control rate of hypertension can reach about 80%, suggesting that the combination of RAS inhibitors and CCB was one of the optimal antihypertensive regimens for hypertensive patients in China [11]. A systematic review based on randomized controlled trials (RCTs) also demonstrated that compared with other antihypertensive treatment options, RAS inhibitors combined with CCB were not only advantageous in the overall study population, but also in the subgroup [12]. The aforementioned research showed that the combination of RAS inhibitors and CCB as a first-line clinical treatment regimen could satisfy patients to a certain extent.

However, hypertension is a complex disease, and the individualized response to drugs is particularly prominent [13,14]. Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) are 2 essential drug classes used to inhibit the RAS system. Studies have shown that even with the same diagnosis, treatment with the same RAS inhibitors could influence blood concentration and efficacy differently [15]. In clinical practice, with the help of a doctor, some patients could find a relatively reasonable medication plan by repeatedly adjusting the medication plan. Even so, some patients still might not attain the desired treatment effect after quantities of adjustments. Although, ACEI+CCB and ARB+CCB are all the first-line clinical treatment scheme in China, there are significant individual differences in the efficacy and side effects between the 2 schemes [16]. Therefore, we designed this real-world study in which we constructed a research cohort of hypertension medications and identified the effects of patient characteristics and comorbid diseases on drug selection, and we proposed a medication selection model under clinical application of renin-angiotensin inhibitor combined with calcium channel blocker (renin-angiotensin inhibitors selection model, RAISM) to provide references for clinical decision-making on antihypertensive medications.

Material and Methods

Study design

This study adopted a non-experimental comparative study design for analysis [17]. Due to the limitation of the research period and clinical resources, in order to reduce the influence of interference factors on research results, a retrospective cohort study method was used. The participants were grouped according to their exposure at a specific point in time (baseline point), and the outcome of participants in each group was observed. This study followed the Helsinki Declaration and was approved by the hospital ethics committee [18]. This study also followed the statement of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [19].

Study data

The study data were derived from the outpatient medical record system of a Chinese National Regional Medical Center from January 2018 to December in 2018. Inclusion criteria was as follows: patient was diagnosed with "hypertension", and the diagnostic criteria for the past year were in accordance with the 2010 Chinese guidelines for the management of hypertension [20]. There was no restriction on patient's age, medical history, or the clinic department where the patient was diagnosed. Exclusion criteria was as follows: continuing hypertensive patient and participant with incomplete data.

Patients received ACEI combined CCB medication plan (abbreviation: ACCB scheme) or ARB combined CCB medication plan (abbreviated: ARCB scheme), and patients were grouped according to their medication status.

Data collection

Data were collected through a 2-personnel independent approach, which were then checked by a third person. For any difference noticed in the collection process, the electronic

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medical record system would be further traced back and confirmed. The fields of data collection included patient medical record number (unique identification code), gender, age, height, weight, outpatient diagnosis, with or without diabetes, renal insufficiency, hyperlipidemia, brain ischemia, and coronary heart disease.

Data processing

According to the patient's medical record number, duplicate patients were removed, and only a patient's latest visit records and data information were retained. The medication scheme of each patient was sorted, and only patients who received the ACCB scheme or ARCB scheme were retained, and patients who had combined ACEI, ARB, and CCB treatment were excluded. The height and weight were converted into body mass index (BMI).

Statistical analysis

All count data included in this study were described in the form of frequency and percentage, and mean and standard deviation were used to represent measurement data; If data met normal distribution, the *t*-test was performed for comparative analysis; If not, the Mann-Whitney U test was used for analysis and comparison; The comparative analysis of the count data was performed using the chi-square test or Fisher's exact probability method. When *P*-value <0.05, the difference was considered to be statistically significant. The logistic regression model was used for univariate and multivariate analysis. According to the parameters of the statistical regression model, a RAISM was established utilizing the nomograph model technology; This study used the C-index and the re-correction curve to evaluate the discriminative ability of the RAISM, and used the receiver operating characteristic (ROC) curve analysis to calculate the cutoff value of the continuous variable, and used the decision curve to evaluate the clinical performance of the RAISM obtained in this study; In multivariate logistic analysis, by assuming that 5 factors were considered to be of clinical importance, and according to criteria that the number of observations was 10 times the number of variables, sample size of this study should not be less than 100 cases; All data analysis used R statistical software, version 3.5.2 (*http://www.r-project.com*).

Results

Clinical characteristics of patients

In this study, 1024 cases were initially retrieved and 213 of them were retained according to the inclusion and exclusion criteria. The case selection process is shown in Figure 1.

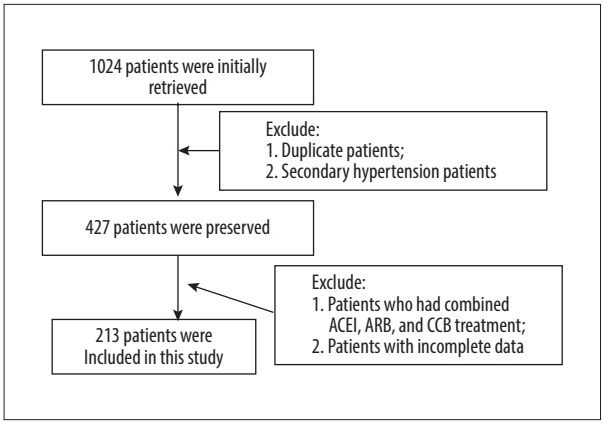

Figure 1. Patient screening process in development a medication selection model.

Patient-related fields were extracted including age, gender, height, weight, BMI, with or without diabetes, renal insufficiency, coronary heart disease, cerebral ischemia, and hyperlipidemia. Among the 213 study patients, 140 patients used ARB+CCB, with an average age of 60.73 years, accounting for 65.73%; 73 patients used ACEI+CCB, with an average age of 52.95 years, accounting for 34.27% (The detailed characteristics of patients are shown in Table 1).

Clinical features and concomitant conditions on drug selection

In order to compare the impact of patient's clinical features and comorbidities on medication choice for hypertension, we used single-factor logistic regression analysis to evaluate variables related to drug selection, including patient characteristics and clinical comorbidity parameters. Results of univariate logistic regression analysis are presented in Table 2. The report format was odds ratio (OR) with 95% confidence interval (CI). In the univariate logistic regression analysis of patient characteristics, age (for years, 0476 [0.319–0.711]), BMI for kg/m^2 (1.274 [1.001–1.622]), and elderly patient (for ≥65 versus <65 years, 0.365 [0.180–0.743]) were the discriminative factors of drug selection; In the univariate logistic regression analysis of clinical comorbidity parameters, diabetes mellitus (for with versus without, 0.471 [0.203–1.092]), renal insufficiency (for with versus without, 0.542 [0.268–1.094]), and hyperlipidemia (for with versus without, 0.270 [0.100–0.728]) were the discriminative factors that influence drug choice.

When BMI was a continuous variable, it was a discriminative factor for drug selection. However, there was no statistical difference between 2 groups when they were divided according to the BMI cutoff of 24 kg/m^2 (overweight) (OR=1.556, 95% CI: 0.856–2.827, *P*=0.147), suggesting that the critical value indicating overweight is not the cutoff value that affects the patient's medication. Therefore, we identified the cutoff value

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Table 1. Participant characteristics (n=213).

	ACEI+CCB (n=73)	ARB+CCB (n=140)	Total (n=213)	*P*-value
Age (years)	52.95±11.99	60.73±14.90	58.06±14.43	0.001
Sex				0.560
Male	39 (53.42%)	82 (58.57%)	121 (56.81%)	
Female	34 (46.58%)	58 (41.43%)	92 (43.19%)	
BMI	24.05±5.64	22.81±3.07	23.24±4.16	0.039
Height (cm)	165.11±6.54	165.37±6.52	165.29±6.51	0.783
Weight (kg)	65.47±15.34	62.55±10.04	63.55±12.16	0.096
Overweight (BMI >24)				0.165
Yes	28 (38.36%)	40 (28.57%)	68 (31.92%)	
No	45 (61.64%)	100 (71.43%)	145 (68.08%)	
Elderly patient (≥65 years)				0.004
Yes	12 (16.44%)	49 (35.00%)	61 (28.64%)	
No	61 (83.56%)	91 (65.00%)	152 (71.36%)	
Diabetes mellitus				0.088
Yes	8 (10.96%)	29 (20.71%)	37 (17.37%)	
No	65 (89.04%)	111 (79.29%)	176 (82.63%)	
Renal insufficiency				0.096
Yes	13 (17.81%)	40 (28.57%)	53 (24.88%)	
No	60 (82.19%)	100 (71.43%)	160 (75.12%)	
Hyperlipidemia				0.006
Yes	5 (6.85%)	30 (21.43%)	35 (16.43%)	
No	68 (93.15%)	110 (78.57%)	178 (83.57%)	
Cerebral ischemia				0.338
Yes	2 (2.74%)	9 (6.43%)	11 (5.16%)	
No	71 (97.26%)	131 (93.57%)	202 (94.84%)	
Coronary disease				0.999
Yes	6 (8.22%)	13 (9.29%)	19 (8.92%)	
No	67 (91.78%)	127 (90.71%)	194 (91.08%)	

ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin receptor antagonist; CCB – calcium channel blocker; BMI – body mass index.

through the ROC curve, and the results showed that the cut-off value of BMI was 23.805 kg/m^2 (Figure 2). To be specific, univariate logistic regression demonstrated that statistical differences appeared between the 2 groups (OR=1.845, 95% CI: 1.02–3.33, *P*=0.042) when divided by the BMI of 23.805 kg/m^2.

Development and validation of a RAISM base on study cohort

All variables in this study were patients' characteristic parameters before medication selection, including demographic characteristics and clinical comorbidity parameters. On the basis of univariate logistic regression analysis, independent factors that influence drug selection were incorporated into the multifactor

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Table 2. Univariate logistic regression analysis of drug selection based on clinical data in the target queue.

Variable	OR	95% CI	*P*-value
Age (years)	0.476	0.319–0.711	<0.001
Sex (Female *vs.* Male)	1.233	0.697–2.179	0.472
BMI	1.274	1.001–1.622	0.049
Height (cm)	0.938	0.607–1.451	0.774
Weight (kg)	1.260	0.952–1.667	0.106
Overweight (>24 *vs.* ≤24)	1.556	0.856–2.827	0.147
Elderly patient (≥65 *vs.* <65 years)	0.365	0.180–0.743	0.005
Diabetes mellitus (yes *vs.* no)	0.471	0.203–1.092	0.079
Renal insufficiency (yes *vs.* no)	0.542	0.268–1.094	0.087
Hyperlipidemia (yes *vs.* no)	0.270	0.100–0.728	0.010
Cerebral ischemia (yes *vs.* no)	0.410	0.086–1.950	0.262
Coronary disease (yes *vs.* no)	0.875	0.318–2.406	0.796
BMI (>23.805 *vs.* <23.805)	1.845	1.021–3.333	0.042

OR – odd ratio; CI – confidence interval; BMI – body mass index.

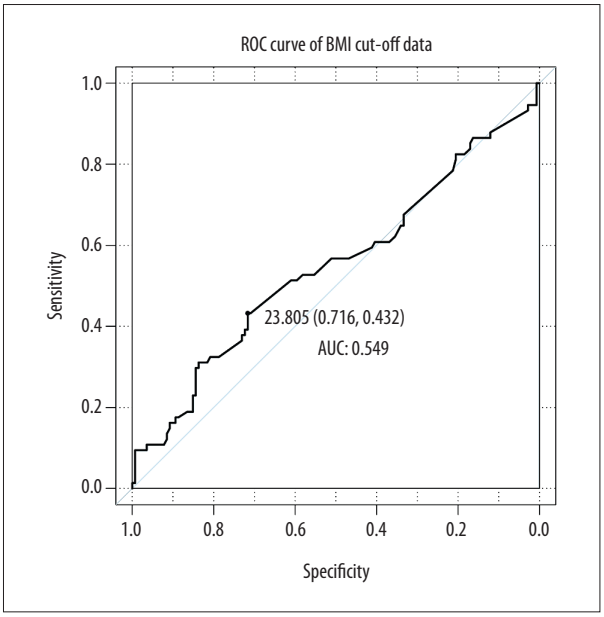

Figure 2. Receiver operating characteristic (ROC) curve of body mass index (BMI) cutoff data in medication selection.

logistic regression analysis, generating the model construction parameters. Through the application of multivariate logistic regression analysis, it was found that the conditions of whether patients were elderly, with or without renal insufficiency, and with or without hyperlipidemia were independent discriminative factors which affect drug selection, and the OR and 95% CI were 0.341 (0.161–0.719), 0.493 (0.234–1.040), and 0.288 (0.103–0.805), respectively, as shown in Table 3.

Model construction parameters were used to generate a RAISM (Table 3). The internal verification was utilized to verify the discriminative ability of the model. The internally verified C-index was 0.699 (0.680–0.718). The calibration curve for the selection and actual results of the RAISM was shown in Figure 3 (Mean squared error=0.002), which indicated that the discriminative ability on the RAISM was good.

Application and clinical manifestations of RAISM

In order to improve the practicality of the RAISM, the Youden index (sensitivity+specificity – 1) was used to calculate the best cutoff value of the nomogram score, and the physicians can refer to the cutoff value to set the threshold probability. The cutoff value under the maximum Youden index was 316 points (the corresponding selection probability is 58%), and under this circumstance, the data of 213 patients were divided into ACCB group and ARCB group, with a sensitivity of 60.3% and a specificity of 73.6%.

The decision curve was further used to compare the net benefit value of the RAISM under various threshold probabilities. The decision curve shown in Figure 4, from which, it can be seen that compared with the 2 extreme cases (assuming that all patients used one treatment regimen or no medication), within the threshold probability range of 21% to 57%, there was a net benefit when implementing medication guidance on the basis of the RAISM.

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Table 3. Multivariate logistic regression analysis of drug selection based on clinical data in the target queue.

Variable	β	OR	95% CI	*P*-value
Elderly patient (≥65 *vs.* <65 years)	–1.076	0.341	0.161–0.719	0.005
Diabetes mellitus (yes *vs.* no)	0.484	0.616	0.251–1.510	0.290
Renal insufficiency (yes *vs.* no)	–0.706	0.493	0.234–1.040	0.063
Hyperlipidemia (yes *vs.* no)	–1.243	0.288	0.103–0.805	0.018
BMI (>23.805 *vs.* <23.805)	0.323	1.382	0.732–2.606	0.318

β – intercept value; OR – odd ratio; CI – confidence interval; BMI – body mass index.

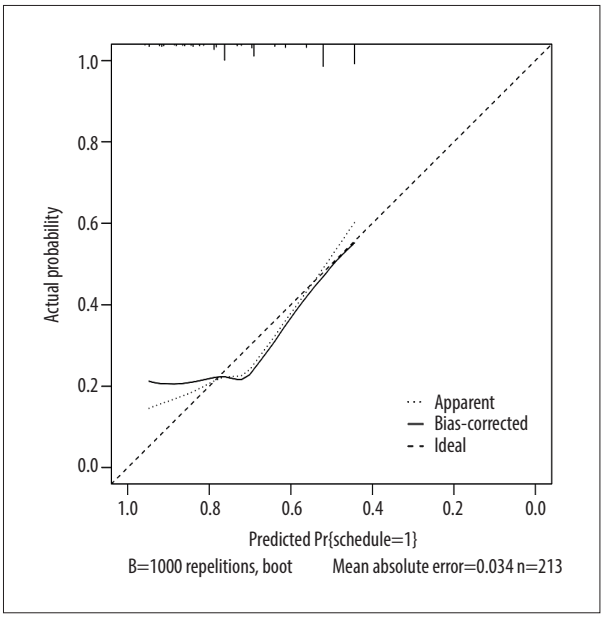

Figure 3. The calibration curve for the selection and actual results of RAISM (renin-angiotensin inhibitors selection model).

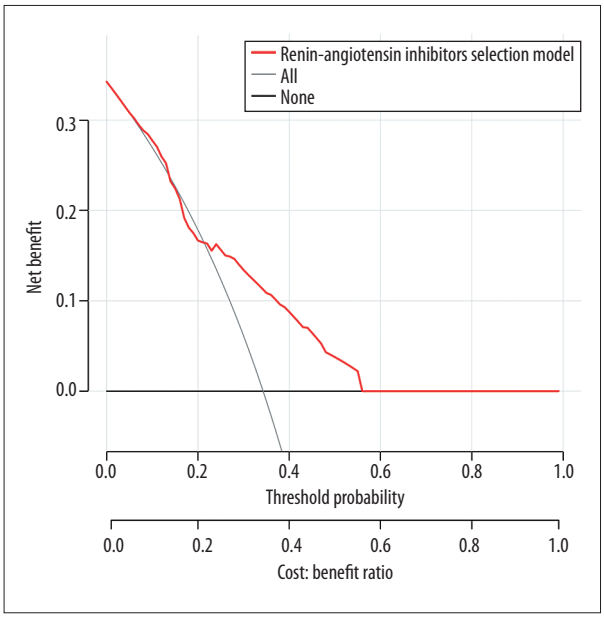

Figure 4. The decision curve of RAISM (renin-angiotensin inhibitors selection model).

Discussion

The regimen of RAS inhibitors combined with CCB has been widely used to treat hypertension, especially for patients with hypertension in combination with diabetes [21]. This regimen was more often recommended for reducing the incidence and mortality of nephropathy and CVDs [22,23]. Based on the results of RCTs, there were differences in the treatment effect between subgroups treated with different RAS inhibitors [24]. Clinically, it is not clear how to choose different RAS inhibitors based on the differences of patient characteristics. Therefore, we designed this real-world study so as to provide a reference for physicians to make a reasonable selection of RAS inhibitors.

In recent years, the establishment of statistical prediction models has become a hot spot in medication clinical studies [25,26]. The nomogram, as a highly individualized visual prediction tool, has been widely adopted in the prediction and decision-making of clinical medication selection and various other important events, including hypertension, diabetes, and nephropathy [27,28]. The main feature of the nomogram is to create a visual graph that can accurately calculate the clinical time probability according to the parameters of the statistical regression model. Therefore, we used the nomogram technique to construct a model for selecting medications for hypertension.

This study established a nomogram model of medication selection on the basis of demographic characteristics and concomitant conditions of both groups of patients who received ACCB and ARCB regimen, respectively. The main findings of this study included: 1) whether the patient was elderly or not, with or without nephropathy, and with or without hyperlipidemia were independent discriminative factors affecting RAS inhibitors selection in hypertensive patients; and 2) the better medication regimen could be determined by using the RAISM based on patients' characteristic score.

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The results of univariate logistic regression analysis indicated that the age, BMI of the patient, and whether he or she was elderly, whether the patient had diabetes, renal insufficiency, or hyperlipidemia were the discriminative factors affecting the choice of hypertension drugs. Results of multivariate logistic regression analysis also suggested that whether the patient was elderly, had renal insufficiency, or hyperlipidemia were the discriminative factors affecting the choice of hypertension drugs. Hence, whether the patient was elderly, accompanied by renal insufficiency, or hyperlipidemia were independent factors that influence the choice of RAS inhibitor drugs. We classified our patients into overweight and non-overweight groups according to the BMI cutoff of 24 kg/m^2, but no statistical difference was detected between the 2 groups [29,30]. Therefore, we further calculated the optimal cutoff value that affects the choice of RAS inhibitor drugs through the ROC curve to be 23.805 kg/m^2. At the same time, considering the co-linear relationship between the patient's age and whether they are senile, and based on the simplicity of the physician's operation, we retained the inclusion parameters of whether the patient is senile.

Based on the model composition parameters attained from logistic regression, whether the patient is senile, whether the BMI is less than 23.805 kg/m^2, whether with diabetes, renal insufficiency and hyperlipidemia, we established a hypertension drug selection nomogram model which could calculate the discrimination probability of drug selection for each patient according to their characteristics and comorbidities. Physicians can conveniently acquire a quantitative medication selection probability based on this medication selection model and determine which therapeutic regimen to choose for the patient. Meanwhile, in order to facilitate the use of the scoring mechanism of the RAISM, we determined the optimal cutoff value of 316 points through the Youden index, as a reference for the physician to judge the threshold probability.

In clinical pharmacology, there some differences in the therapeutic targets of different RAS inhibitors, which will inevitably lead to certain differences in clinical application [31]. The mechanism of ACEI is to inhibit RAS system and the conversion from angiotensin I (Ang I) to Ang II, to reduce the level of Ang II in plasma, reducing the secretion of aldosterone and the retention of water and sodium in the body, inducing the increase of prostacyclin (PGI2) and intravascular nitric oxide (NO), so as to achieve dilating blood vessels, reducing peripheral circulation resistance, cardiac anteroposterior load, proteinuria and improving renal blood flow [32,33]. ARB works by blocking AT1 in the 4 Ang II receptor subtypes (AT1, AT2, AT3, and AT4) to inhibit vasoconstriction and myocardial contraction, to reduce pituitary hormones, aldosterone secretion, and water and sodium retention [34,35]. Current drug treatment for hypertension is based more on the evidence at population level. There are no clear guidelines for the selection of ACCB or ARCB in clinical guidelines [36]. In most cases, if patients use one drug and if found to be intolerant, will then be changed to another drug. Therefore, rational application of RAS inhibitors accomplished through individualized methods has certain guiding significance for clinical practice.

Real-world data have become an important source of evidence for healthcare decisions [37]. In 2018, the US FDA incorporated real-world research evidence into the drug approval process [38]. In 2019, the China Drug Evaluation Center drafted the "Basic Considerations of Real-World Evidence Supporting Drug Development (Draft for Comment)" to estimate the use of real-world evidence in evaluating the application scenarios and principles of drug effectiveness and safety. This study provides clinical reference through real-world research design; it used the C-index to evaluate the predictive power of the RAISM. The results suggested that the RAISM established in this study predicted a C-index of 0.699 in all samples, which was good. The actual occurrence and predicted occurrence are fairly consistent. The decision curve analysis showed that within the threshold probability range of 21–57%, the application of a RAISM would bring net benefit. The above analysis results have repeatedly confirmed that the RAISM provided by this study has reference value for the drug decision for RAS inhibitors.

There are some limitations in this study. Firstly, this study was a single-center study, so that certain homogeneity might exist among the hypertensive patients, and more RCTs and multi-center studies are required to verify the results of this study. Secondly, this study was a retrospective study, which means the sequential order of exposure and outcome was unavailable, and the causal relationship could not be determined. Therefore, this study did not make judgment on the treatment outcome of different medication regimens. The rationality of medication was based on the rationality of prescription, and bias might exist in the results. Thirdly, this study lacked information on blood pressure monitoring data, and we only considered the complication data of heart, brain, kidney, and vascular. Further prospective studies are needed to validate the results of this study.

Conclusions

In summary, whether the patient was senile, with or without renal insufficiency, and with or without hyperlipidemia were independent discriminative factors that affect the clinical selection of different medication regimens for RAS inhibitors combined CCB. In addition, the RAISM established based on nomogram technology has good predictive power and can bring clinical net benefits, but RCTs and multi-center studies are required to confirm this conclusion.

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Trial registration

This study was registered at www.chictr.org as a primary register of the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), and the registered number is ChiCTR1900026339.

Ethics approval

Required ethics approvals have been obtained prior to our study from the ethics committee of the First Affiliated Hospital of College of Medicine of Zhejiang University in China, and the ethical approval number was #2019-1391.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest

None.

References:

1. Frieden TR, Jaffe MG: Saving 100 million lives by improving global treatment of hypertension and reducing cardiovascular disease risk factors. J Clin Hypertens (Greenwich), 2018; 20(2): 208–11
2. Ettehad D, Emdin CA, Kiran A et al: Blood pressure lowering for prevention of cardiovascular disease and death: A systematic review and meta-analysis. Lancet, 2016; 387(10022): 957–67
3. Forouzanfar MH, Liu P, Roth GA et al: Global burden of hypertension and systolic blood pressure of at least 110 to 115 mmHg, 1990–2015 [published correction appears in JAMA, 2017; 317(6): 648]. JAMA, 2017; 317(2): 165–82
4. Joint Committee for Guideline Revision: 2018 Chinese Guidelines for Prevention and Treatment of Hypertension – A report of the Revision Committee of Chinese Guidelines for Prevention and Treatment of Hypertension. J Geriatr Cardiol, 2019; 16(3): 182–241
5. Li Y, Yang L, Wang L et al: Burden of hypertension in China: A nationally representative survey of 174,621 adults. Int J Cardiol, 2017; 227: 516–23
6. Wang Y, Peng X, Nie X et al: Burden of hypertension in China over the past decades: Systematic analysis of prevalence, treatment and control of hypertension. Eur J Prev Cardiol, 2016; 23(8): 792–800
7. Streit S, Gussekloo J, Burman RA et al: Burden of cardiovascular disease across 29 countries and GPs' decision to treat hypertension in oldest-old. Scand J Prim Health Care, 2018; 36(1): 89–98
8. Redwood H: Hypertension, society, and public policy. European Heart Journal Supplements, 2007;9: B13–18
9. Yang T, Xu C: Physiology and pathophysiology of the intrarenal renin-angiotensin system: An update. J Am Soc Nephrol, 2017; 28(4): 1040–49
10. Williams B, Mancia G, Spiering W et al: 2018 ESC/ESH Guidelines for the management of arterial hypertension [published correction appears in Eur Heart J, 2019; 40(5): 475]. Eur Heart J, 2018; 39(33): 3021–104
11. Wang W, Ma LY, Liu MB et al: [Effects of amlodipine plus telmisartan or amlodipine plus amiloride regimen on blood pressure control in hypertensive patients: preliminary report of Chinese Hypertension Intervention Efficacy (CHIEF) trial]. Zhonghua Xin Xue Guan Bing Za Zhi, 2009; 37(8): 701–7 [in Chinese]
12. Huang RS, Cheng YM, Zeng XX et al: Renoprotective effect of the combination of renin-angiotensin system inhibitor and calcium channel blocker in patients with hypertension and chronic kidney disease. Chin Med J (Engl), 2016;129(5): 562–69
13. Evangelou E, Warren HR, Mosen-Ansorena D et al: Genetic analysis of over 1 million people identifies 535 new *loci* associated with blood pressure traits [published correction appears in Nat Genet, 2018; 50(12): 1755]. Nat Genet, 2018; 50(10): 1412–25
14. Zhu X, Feng T, Tayo BO et al: Meta-analysis of correlated traits via summary statistics from GWASs with an application in hypertension. Am J Hum Genet, 2015; 96(1): 21–36
15. Catalá-López F, Macías Saint-Gerons D, González-Bermejo D et al: Cardiovascular and renal outcomes of renin-angiotensin system blockade in adult patients with diabetes mellitus: A systematic review with network meta-analyses [published correction appears in PLoS Med, 2016; 13(6): e1002064]. PLoS Med, 2016; 13(3): e1001971
16. Messerli FH, Bangalore S, Bavishi C, Rimoldi SF: Angiotensin-converting enzyme inhibitors in hypertension: To use or not to use? J Am Coll Cardiol, 2018; 71(13): 1474–82
17. Richters A, Melis RJF: Quasi-experimental study designs: Making a case for non-experimental designs in the spectrum. J Clin Epidemiol, 2017; 91: 146
18. Arie S: Revision of Helsinki declaration aims to prevent exploitation of study participants. BMJ, 2013; 347: f6401
19. von Elm E, Altman DG, Egger M et al: The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for reporting observational studies. Int J Surg, 2014; 12(12): 1495–99
20. Liu LS; Writing Group of 2010 Chinese Guidelines for the Management of Hypertension. [2010 Chinese guidelines for the management of hypertension]. Zhonghua Xin Xue Guan Bing Za Zhi, 2011; 39(7): 579–615 [in Chinese]
21. Shen T, Wang J, Yu Y, Yu J: Comparison of real-world effectiveness between valsartan and non-RAS inhibitor monotherapy on the incidence of new diabetes in Chinese hypertensive patients: An electronic health recording system-based study. Clin Exp Hypertens, 2019; 41(3): 244–54
22. Tsai MS, Tang CH, Lin CY et al: Diuretic or beta-blocker for hypertensive patients already receiving ACEI/ARB and calcium channel blocker. Cardiovasc Drugs Ther, 2017; 31(5–6): 535–43
23. Chin JH, Moon YJ, Jo JY et al: Association between postoperatively developed atrial fibrillation and long-term mortality after esophagectomy in esophageal cancer patients: An observational study. PLoS One, 2016; 11(5): e0154931
24. Potier L, Roussel R, Elbez Y et al: Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in high vascular risk. Heart, 2017; 103(17): 1339–46
25. Osborn DP, Hardoon S, Omar RZ et al: Cardiovascular risk prediction models for people with severe mental illness: Results from the prediction and management of cardiovascular risk in people with severe mental illnesses (PRIMROSE) research program. JAMA Psychiatry, 2015; 72(2): 143–51
26. Meyer A, Svinicki D, Arbinger B et al: Machine learning for real-time prediction of complications in critical care: A retrospective study. Lancet Respir Med, 2018; 6(12): 905–14
27. Zhang YF, Ji H, Lu HW et al: Postoperative survival analysis and prognostic nomogram model for patients with portal hypertension. World J Gastroenterol, 2018; 24(39): 4499–509
28. Minichmayr IK, Roberts JA, Frey OR et al: Development of a dosing nomogram for continuous infusion meropenem in critically ill patients based on a validated population pharmacokinetic model. J Antimicrob Chemother, 2018; 73(5): 1330–39
29. Lin WY, Tsai SL, Albu JB et al: Body mass index and all-cause mortality in a large Chinese cohort. CMAJ, 2011; 183(6): E329–36
30. Zheng W, McLerran DF, Rolland B et al: Association between body-mass index and risk of death in more than 1 million Asians. N Engl J Med, 2011; 364(8): 719–29
31. Mirabito Colafella KM, Bovée DM, Danser AHJ: The renin-angiotensin-aldosterone system and its therapeutic targets. Exp Eye Res, 2019; 186: 107680

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32. Strauss MH, Hall AS: The divergent cardiovascular effects of angiotensin converting enzyme inhibitors and angiotensin receptor blockers on myocardial infarction and death. Prog Cardiovasc Dis, 2016; 58(5): 473–82
33. Gryglewski RJ, Chłopicki S, Uracz W, Marcinkiewicz E: Significance of endothelial prostacyclin and nitric oxide in peripheral and pulmonary circulation. Med Sci Monit, 2001; 7(1): 1–16
34. Onozato ML, Tojo A, Goto A et al: Oxidative stress and nitric oxide synthase in rat diabetic nephropathy: Effects of ACEI and ARB. Kidney Int, 2002; 61(1): 186–94
35. Corvol P, Plouin PF: [Angiotensin II receptor blockers: Current status and future prospects]. Drugs, 2002; 62(Spec No 1): 53–64 [in French]
36. Kharbanda EO, Asche SE, Sinaiko AR et al: Clinical decision support for recognition and management of hypertension: A randomized trial. Pediatrics, 2018; 141(2): e20172954
37. Miksad RA, Abernethy AP: Harnessing the power of real-world evidence (RWE): A checklist to ensure regulatory-grade data quality. Clin Pharmacol Ther, 2018; 103(2): 202–5
38. Hall-Lipsy E, Barraza L, Robertson C: Practice-based research networks and the mandate for real-world evidence. Am J Law Med, 2018; 44(2–3): 219–36

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